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(54) Title
NEW CEPHALOSPORINS CONTAINING, IN POSITION 3, A PROPENYL RADICAL SUBSTITUTED BY A QUARTERNARY AMMONIUM, THEIR PREPARATION PROCESS, THEIR USE AS MEDICAMENTS, THE COMPOSITIONS CONTAINING THEM AND THE INTERMEDIATES OBTAINED

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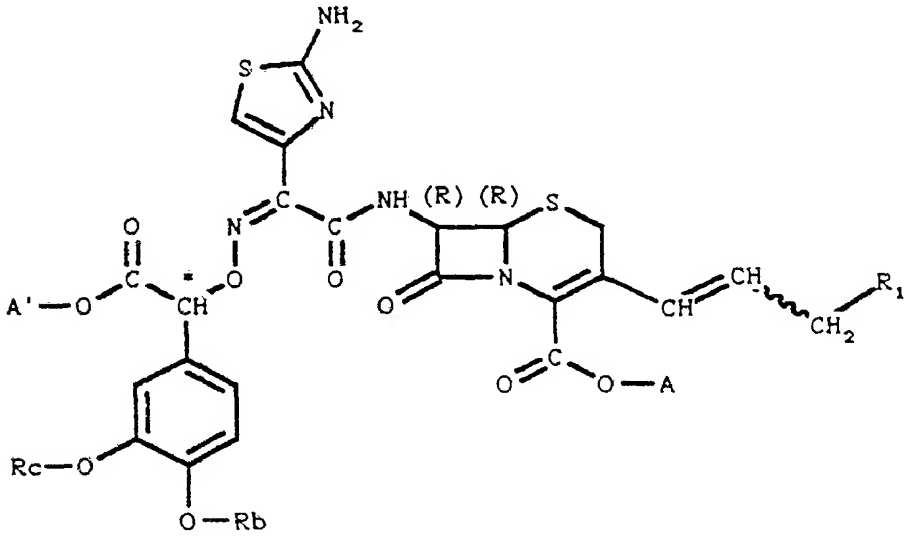
(56) Prior Art Documents
AU 58940/90 C07D 501/22 C07D 501/24
GB 2134522
GB 2157293

(57) Claim

1.- The products of general formula (I):

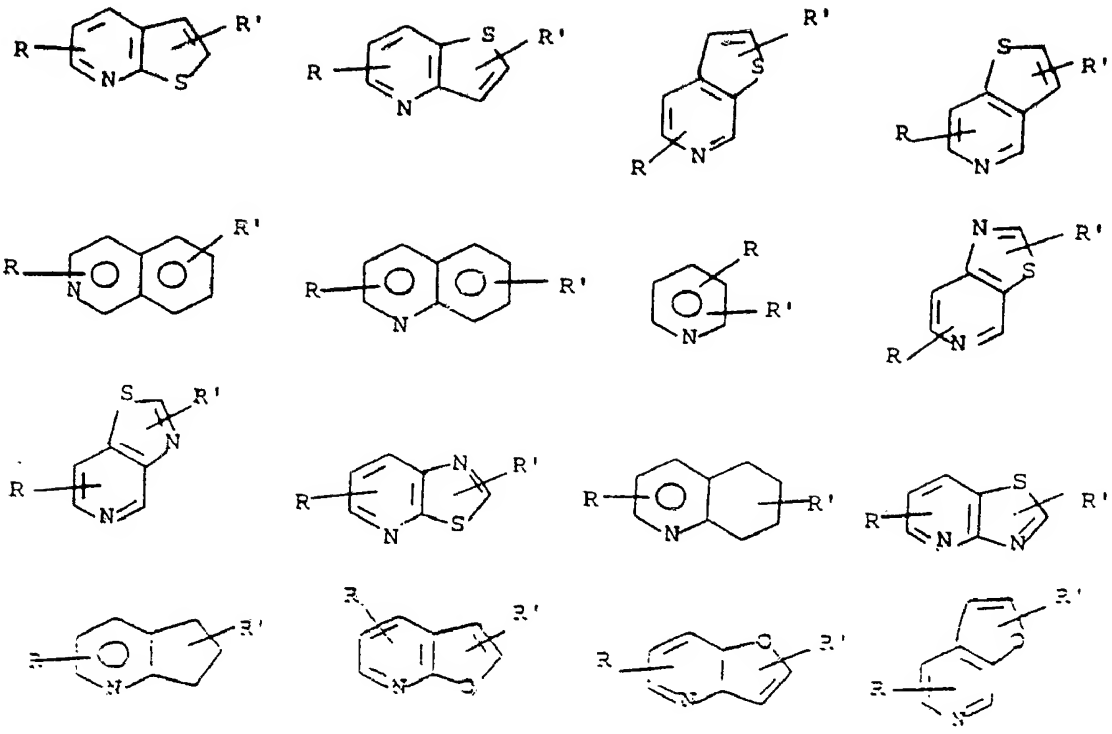


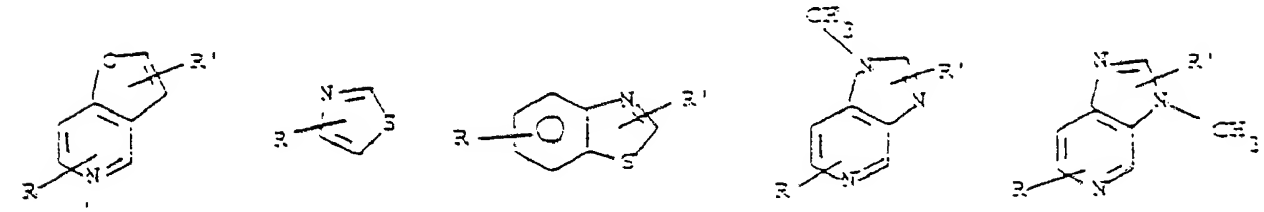
(I)

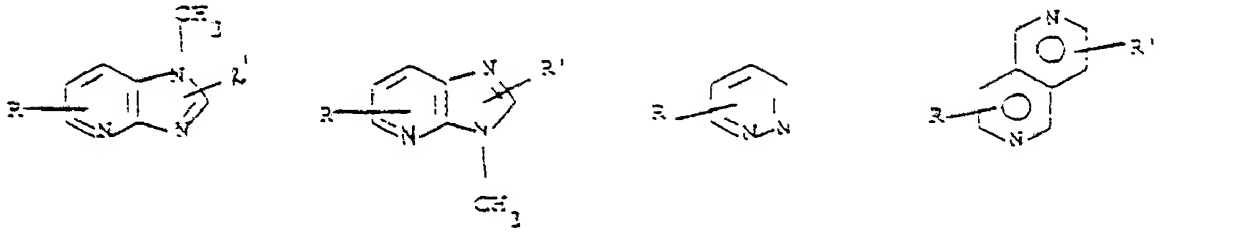
SYN isomer

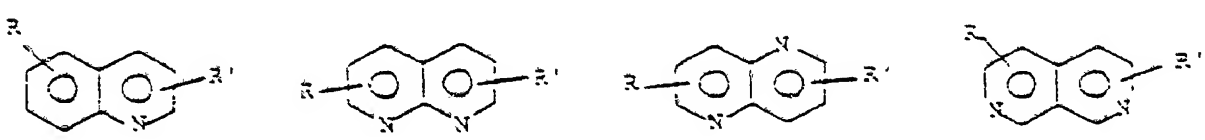
syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:

R_1 represents a radical chosen from the following radicals: ./2









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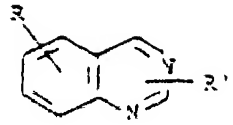
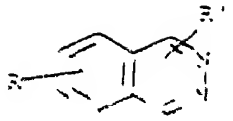
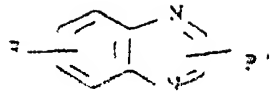
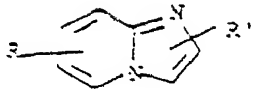
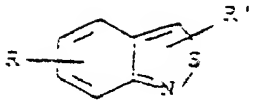
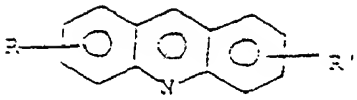
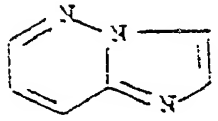
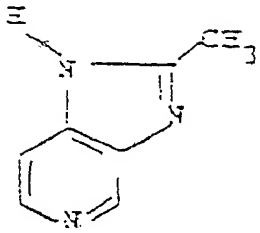
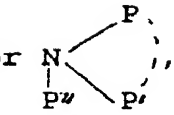
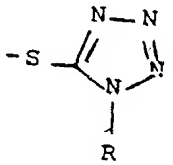
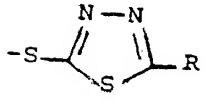
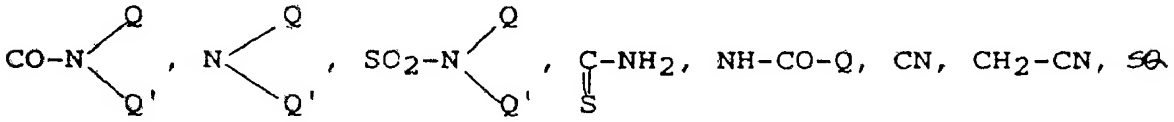




or  , in the quaternary ammonium form or

in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a CO_2-Q,



CH_2-SQ in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P '', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, a saturated heterocycle with 5 or 6 links.

...4

R_b and R_c, identical or different, represent a hydrogen atom or an acyl group,
A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A' represent the remainder of an easily cleavable ester group or CO_2A represents $CO_2^{\ominus}$; the wavy line means that the CH_2R_1 group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids.

AUSTRALIA

PATENTS ACT 1952

643289

Form 10

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

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Int. Cl:

Application Number:
Lodged:

Complete Specification - Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

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Address of Applicant: 35 Boulevard des Invalides, 75007, PARIS, France

Actual Inventors: Jozsef ASZODI
Jean-François CHANTOT
Solange GOUIN D'AMBRIERES

Address for Service: CALLINAN LAWRIE, Patent Attorneys, 278 High Street, Kew, Victoria 3101, Australia.

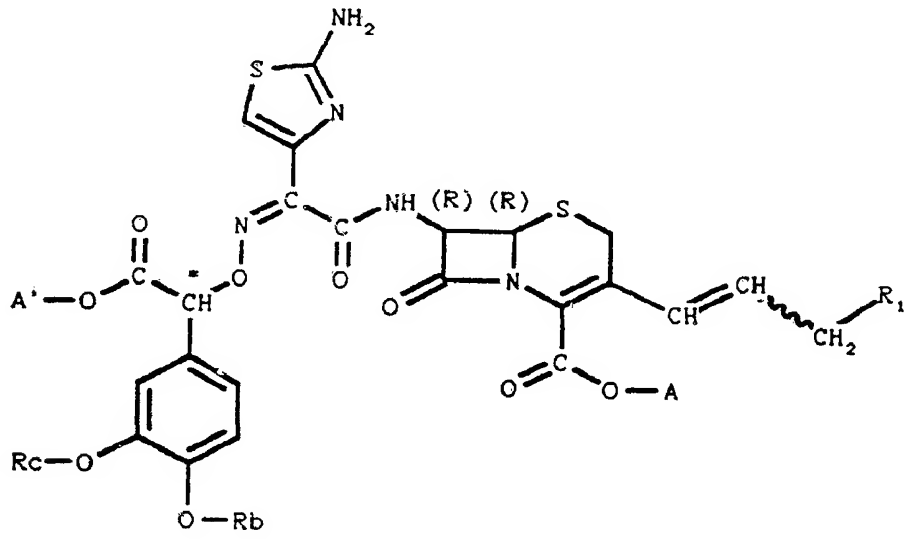
Complete Specification for the invention entitled: **NEW CEPHALOSPORINS CONTAINING, IN POSITION 3, A PROPENYL RADICAL SUBSTITUTED BY A QUATERNARY AMMONIUM, THEIR PREPARATION PROCESS, THEIR USE AS MEDICAMENTS, THE COMPOSITIONS CONTAINING THEM AND THE NEW INTERMEDIATES OBTAINED.**

The following statement is a full description of this invention, including the best method of performing it known to me:-

New cephalosporins containing, in position 3, a propenyl radical substituted by a quaternary ammonium, their preparation process, their use as medicaments, the compositions containing them and the new intermediates obtained.

The present invention relates to new cephalosporins containing, in position 3, a propenyl radical substituted by a quaternary ammonium, their preparation process, their use as medicaments, the compositions containing them and the new intermediates obtained.

A subject of the invention is the products of general formula (I):

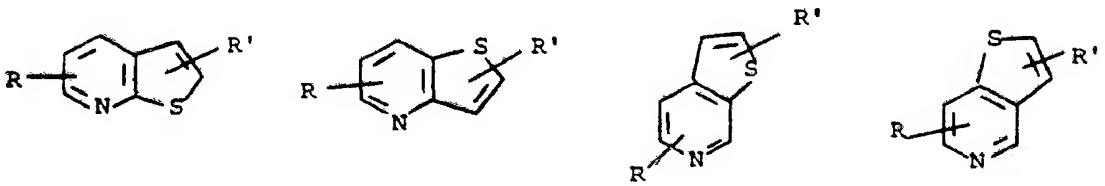


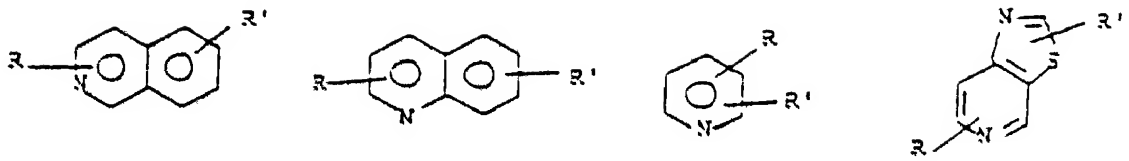
(I)

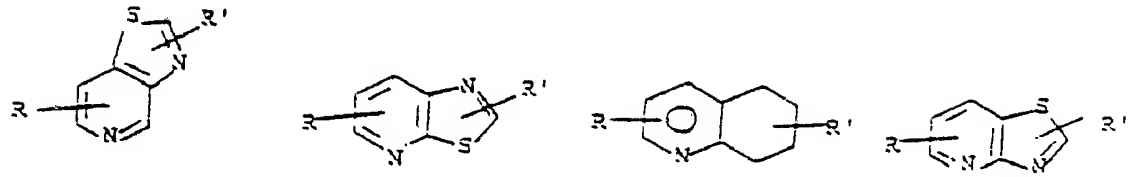
SYN isomer

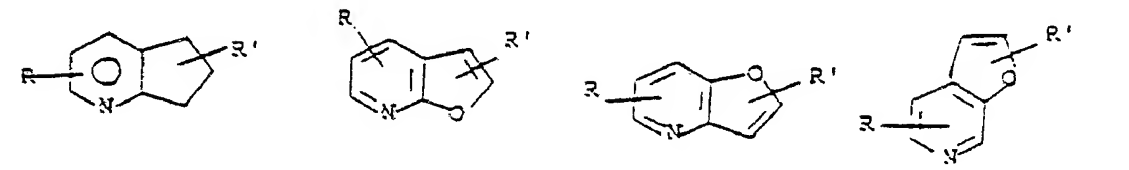
syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:

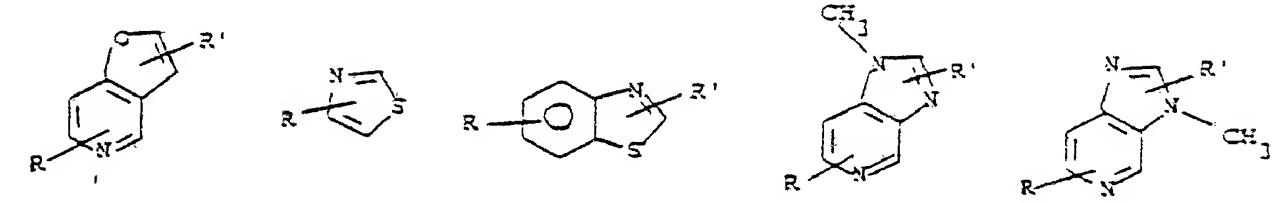
R_1 represents a radical chosen from the following radicals:

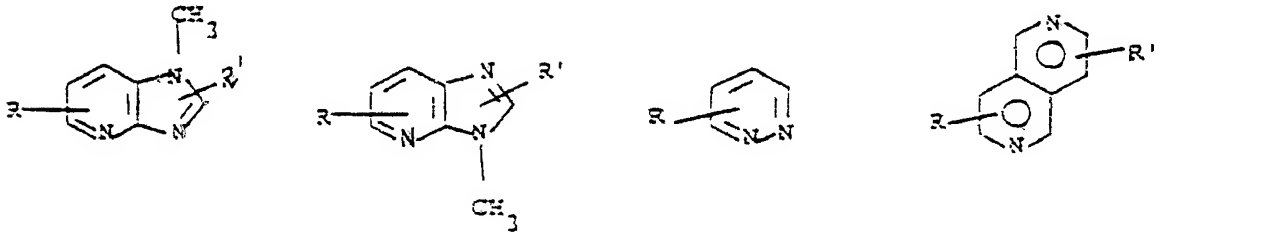


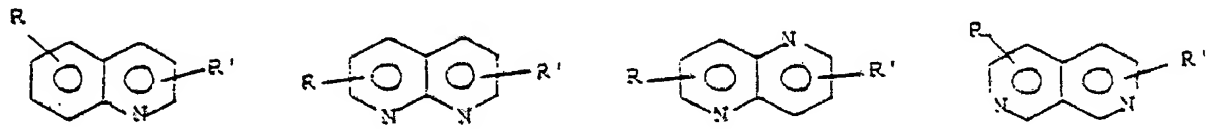


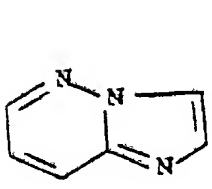


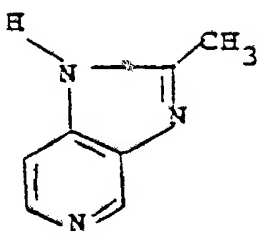


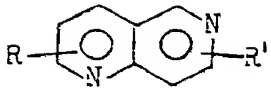


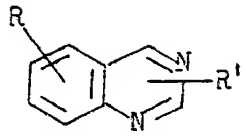


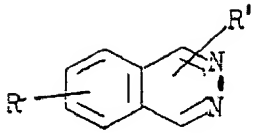


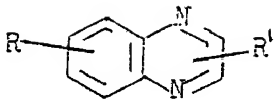


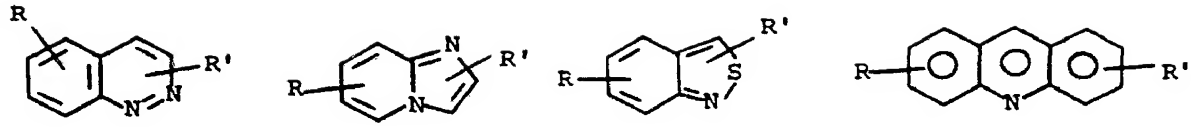


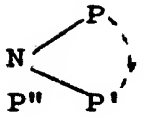

R
N
N
R'


R
N
N
R'

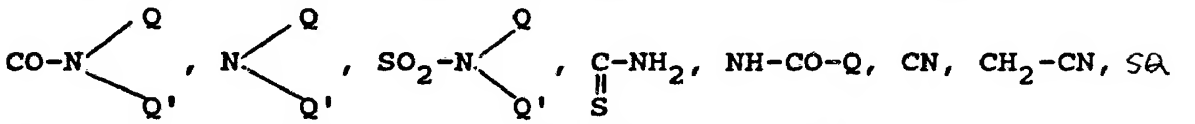

R'
N
N
R


N
N
R
R'



or  , in the quaternary ammonium form or

in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a CO_2-Q,



CH_2-SQ in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P ", identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol) indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, a saturated heterocycle with 5 or 6 links.

R_b and R_c, identical or different, represent a hydrogen atom or an acyl group,

A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A'

represent the remainder of an easily cleavable ester group or CO_2A represents $CO_2^{\ominus}$; the wavy line means that the CH_2R_1 group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids.

By alkyl radical containing 1 to 4 carbon atoms, is meant, for example, methyl, ethyl, propyl, isopropyl, butyl, linear or branched.

When P and P' form a heterocycle with the nitrogen atom to which they are linked, it can be a pyrrolidine, a morpholine or a piperidine.

When R_b and/or R_c represent an acyl radical, it can be an acetyl, propionyl or benzoyl radical. It can also be the other acyl value mentioned hereafter. The preferred acyl value is the acetyl value. The preferred value for R_b and R_c is the hydrogen value.

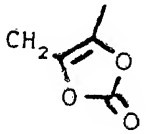
Among the values of A and A' there can be mentioned an equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium. Among the organic bases there can be mentioned methylamine, propylamine, trimethylamine, diethylamine, triethylamine, N,N-dimethylethanolamine, tris[(hydroxymethyl)-amino]-methane, ethanolamine, pyridine, picoline, dicyclohexylamine, morpholine, benzylamine, procaine, lysine, arginine, histidine, N-methylglucamine.

Among the other remainders of easily cleavable ester groups that can be represented by A and A', the following groups can be mentioned: methoxymethyl, ethoxymethyl, isopropyloxymethyl, alpha-methoxy ethyl, alpha-ethoxy ethyl, methyl-thiomethyl, ethylthiomethyl, isopropylthiomethyl, pivaloyloxymethyl, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, isobutyryloxymethyl, valeryloxymethyl, isovaleryloxymethyl, tert-butylcarbonyloxymethyl, hexadecanoyloxymethyl, propionyloxyethyl, isovaleryloxyethyl, 1-acetyloxy-ethyl, 1-propionyloxyethyl, 1-butyryloxyethyl, 1-tertbutylcarbonyloxyethyl, 1-acetyloxypropyl, 1-hexadecanoyl-oxyethyl, 1-propionyloxypropyl, 1-methoxycarbonyloxyethyl, methoxycarbonyloxymethyl, 1-acetyloxybutyl, 1-acetyloxyhexyl, 1-acetyloxyheptyl, phthalidyl, 5,6-dimethoxyphthalidyl, tert-butylcarbonylmethyl, allyl, 2-chloroallyl,

methoxycarbonylmethyl, benzyl or tert-butyl.

Among the other remainders of ester groups that can be represented by A and A', the following groups can be mentioned: methoxyethoxymethyl, dimethylaminoethyl, cyanomethyl, tert-butoxycarbonylmethyl, 2,2-ethylenedioxyethyl, cyanoethyl, 2,2-dimethoxyethyl, 2-chloroethoxymethyl, 2-hydroxyethoxy-ethyl, 2,3-epoxypropyl, 3-dimethylamino, 2-hydroxypropyl, 2- hydroxyethyl, 2-methylaminoethoxymethyl, 2-aminoethoxymethyl, 3-methoxy-2,4-thiadiazol-5-yl, 2-tetrahydropyrannyl, 1-methoxy-1-methylethyl, 2-hydroxy-1-methyl-ethyl, isopropyl, carbamoylmethyl, chloromethyl, 2-chloroethyl, acetylmethyl, 2-methylthioethyl or thiocyanatomethyl.

Among the other remainders of ester groups that can be represented by A and A', the following groups can be mentioned: 2-chloro-1-acetyloxyethyl, 2-bromo-1-acetyloxyethyl, 2-fluoro-1-acetyloxyethyl, 2-methoxy-1-acetyloxyethyl, 2-methyl-1-acetyloxypropyl, 1-methyl-1-acetyloxyethyl, 1-methoxyacetyloxyethyl, 1-acetylcarbonyloxyethyl, 1-hydroxyacetyloxyethyl, 1-formylcarbonyloxyethyl, 1-(2-thienyl)-carbonyloxyethyl, 1-(2-furyl)-carbonyloxyethyl, 1-(5-nitro-2-furyl)-carbonyloxyethyl, 1-(2-pyrrolyl)-carbonyloxyethyl, 1-(propionyloxycarbonyloxy)-ethyl, 1-(propyloxycarbonyloxy)-ethyl, 1-(isopropyloxycarbonyloxy)-ethyl, 1-(methoxyethoxycarbonyloxy)-ethyl, 1-(allyloxycarbonyloxy)-ethyl, isopropyloxycarbonyl-methyl, 1-[(2,3-epoxypropyl)-oxycarbonyloxy]-ethyl, 1-[(2-furyl)-methyloxycarbonyloxy]-ethyl, 1-(2-fluoro-ethyl)-oxycarbonyloxyethyl, 1-(methoxycarbonyloxy)-propyl, 1-(methoxycarbonyloxy)-1-methyl-ethyl, (methoxycarbonyloxy)-chloromethyl, 1-(methoxycarbonyloxy)-2-chloroethyl, 1-(methoxycarbonyloxy)-2-methoxy-ethyl, 1-(methoxycarbonyloxy)-allyl, or a remainder



The products of formula (I) can also be presented in the form of organic or mineral acid salts.

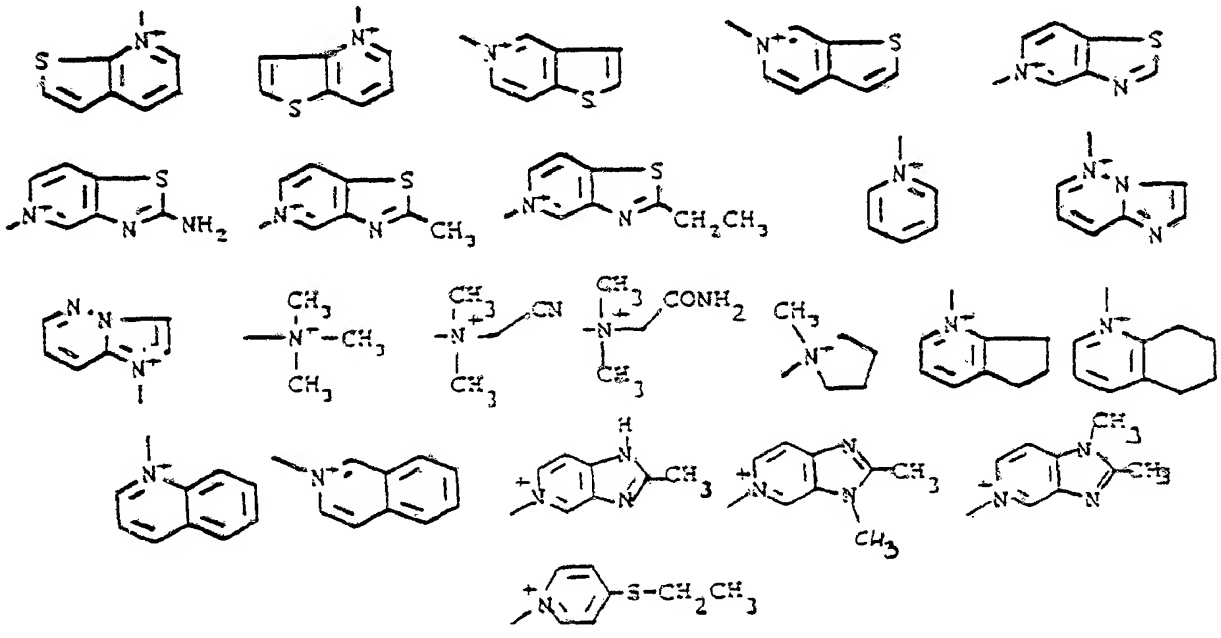
Among the acids with which the amino group or groups of products (I) can be salified, there can be mentioned among others the following acids: acetic, trifluoroacetic, maleic, tartaric, methanesulphonic, benzenesulphonic, paratoluenesulphonic, phosphoric, sulphuric, hydrochloric, hydrobromic, hydroiodic.

The products can also be presented in the form of internal salts.

In a preferred method of the invention, A' represents a hydrogen or sodium atom, preferably hydrogen and CO_2A represents $CO_2^{\ominus}$.

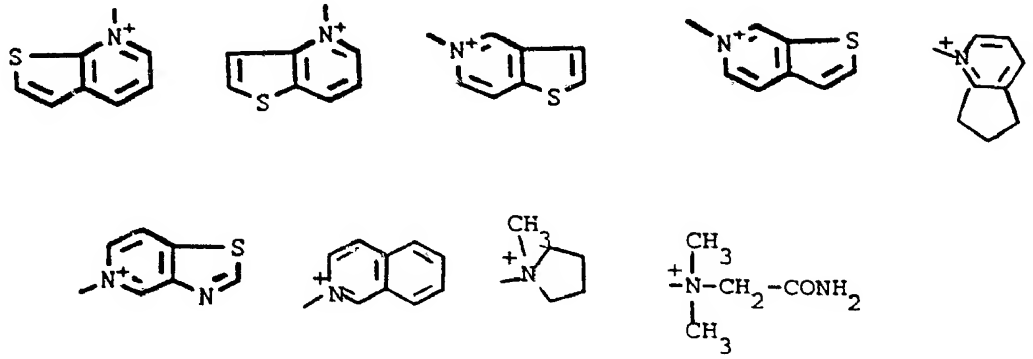
The expression in the form of quaternary ammonium indicates that the R_1 radical is linked by the nitrogen atom or one of the nitrogen atoms that it contains.

Particularly a subject of the invention is the products of general formula (I) as defined above in which R_1 is chosen from the following radicals:

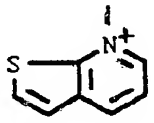


More particularly a subject of the invention is the

products of general formula (I) as defined above in which R_1 is chosen from the following radicals:



preferably the radical:



Quite particularly a subject of the invention is the products described hereafter in the examples, namely:
- [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,
- [6R-[3(E),6alpha, 7beta(Z)]]-7-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters and particularly in the S form,
- [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-

[4,2,0]-oct-2-en-3-yl]-2-propenyl] isoquinolinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2 amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium in the R or S form or the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

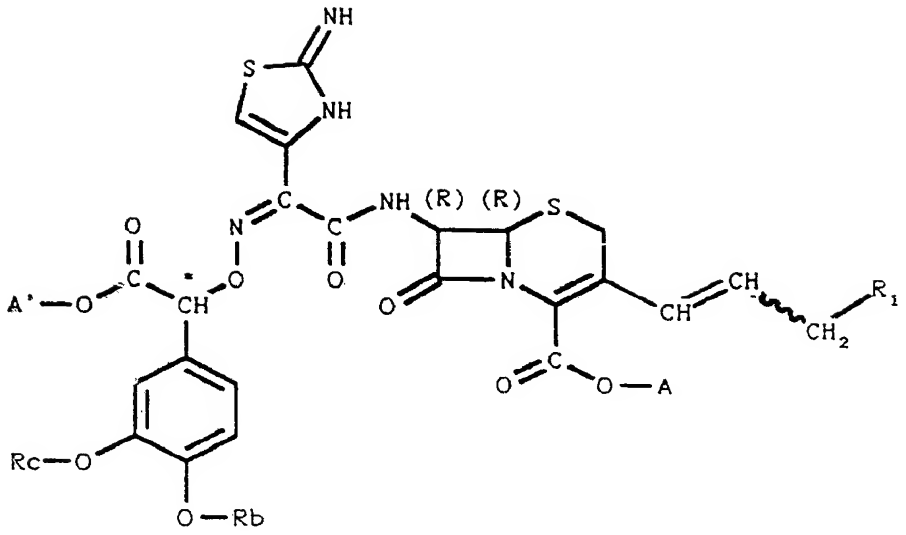
- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyrindinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters.

It is understood that the aforementioned products of formula (I) can exist:

either in the form indicated by said formula (I),

or in the form of products of formula $(I)_Z$:

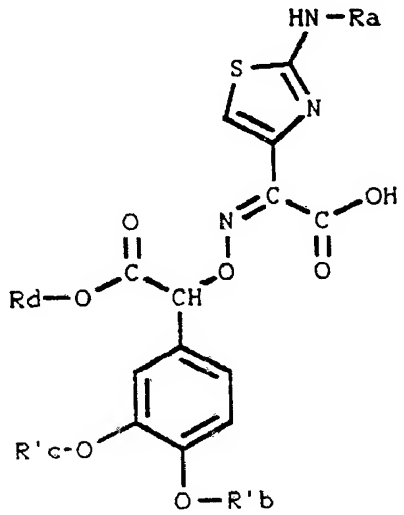


(I)Z

SYN isomer

in which A, A', R_1, R_b and R_c have the previous meaning.

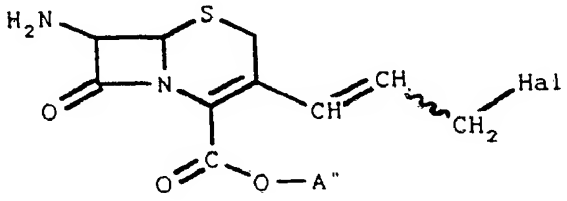
Also a subject of the invention is a preparation process for the products of formula (I) as defined above, characterized in that a product of formula (II):



(II)

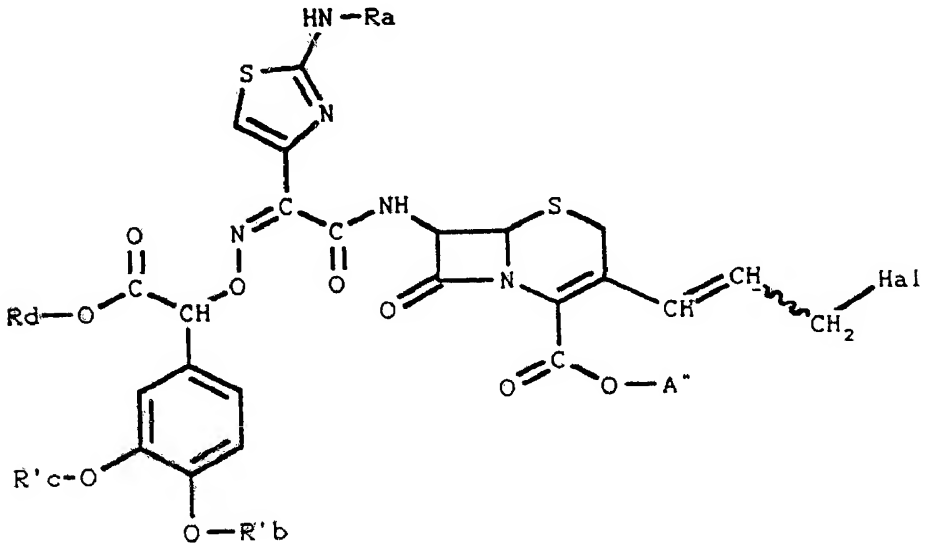
racemic or optically active syn isomer or a functional

derivative of the product of formula (II), in which R_a represents a hydrogen atom or a protective group of the amino radical, R'_b and R'_c, identical or different, represent a hydrogen atom or a protective group of the hydroxyl radical, R_d represents a hydrogen atom or the remainder of an easily eliminable ester group, is reacted with a product of formula (III):



(III)

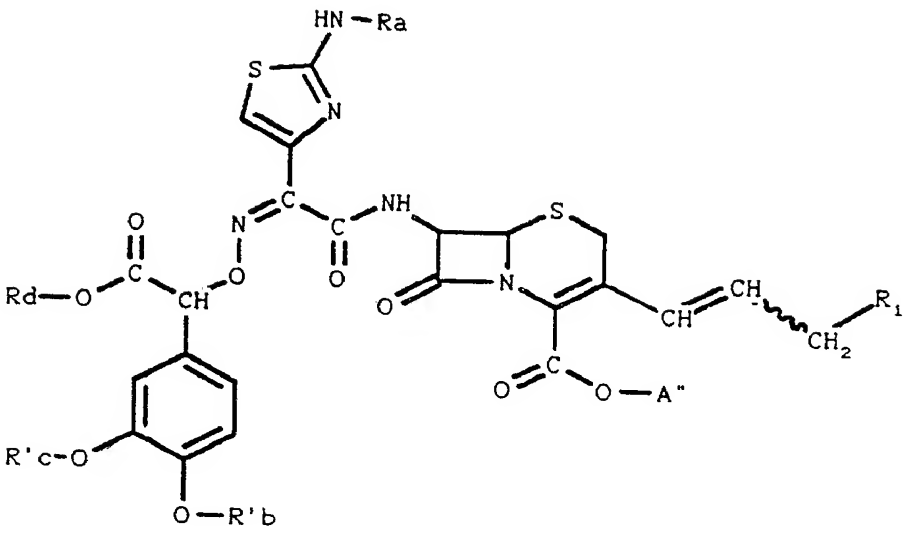
in which Hal represents a halogen atom, A" represents a hydrogen atom or the remainder of an easily eliminable ester group and the wavy line indicates that the CH_2Hal group can be found in E or Z position, in order to obtain a product of formula (IV):



(IV)

which is reacted with a reagent capable of introducing the R_1

radical in order to obtain a product of formula (V):



(V)

which, if desired, is separated into its E or Z isomers or the Z isomers are converted into E isomers and which products of formula (V), if necessary or if desired, are subjected to one or more of the following reactions, in any order:

a) cleaving, by hydrolysis or by the action of the thiourea, of all or part of the ester groups or protective groups of the amino radical or the hydroxyl radicals,

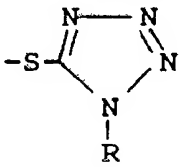
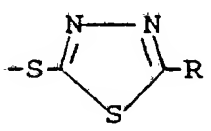
b) esterification or salification of the carboxylic radical or radicals by a base,

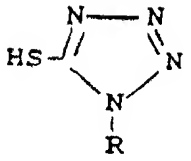
c) salification of the amino radical by an acid,

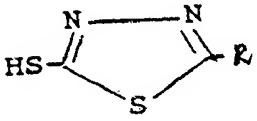
d) separation of products in the form of an R, S mixture into R or S.

By reagent capable of introducing the R_1 radical, is meant:

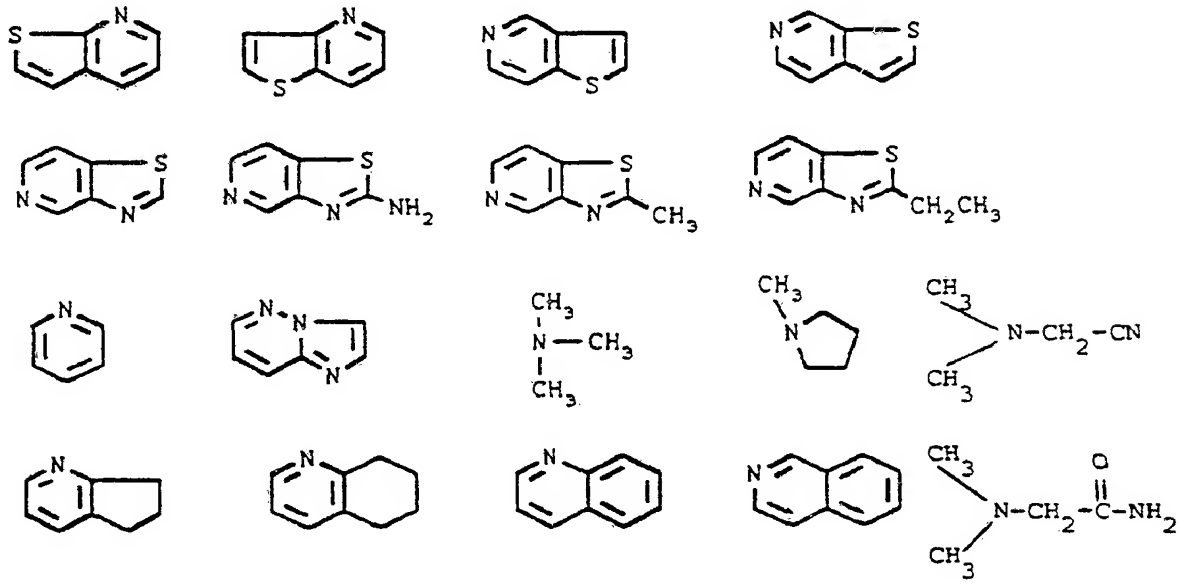
<u>either</u> when R_1 represents a quaternary ammonium, a reagent composed of the R_1 radical itself, this not being in the form of quaternary ammonium; notably if one wishes to introduce a pyridinium radical, the operation will be done with pyridine,

<u>or</u> when R_1 represents  or  ,

a reagent corresponding respectively to  or

 or preferably its sodium salt.

Among the preferred reagents, there can also be mentioned those corresponding to the formulae:



In addition to the groups mentioned above, the easily eliminable ester groups which can be represented by A" and R_d can be for example the ester formed with the following radicals: butyl, isobutyl, tert-butyl, pentyl, hexyl, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, 2-acetoxyethyl, 2-propionyloxyethyl, 2-butyryloxyethyl.

The following radicals can also be mentioned: 2-

iodoethyl, 2,2,2-trichloroethyl, vinyl, allyl, ethynyl, propynyl, benzyl, 4-methoxybenzyl, 4-nitrobenzyl, phenylethyl, trityl, diphenylmethyl, 3,4-dimethoxyphenyl.

The following radicals can also be mentioned: phenyl, 4-chlorophenyl, tolyl, tert-butylphenyl.

The diphenylmethyl radical is preferred for R_d and the 4-methoxybenzyl or diphenylmethyl radical is preferred for A".

The protective group of the amino radical which can be represented by R_a can be for example, an alkyl radical with 1 to 6 carbon atoms such as, preferably, tert-butyl or tert-amyl.

R_a can also represent an aliphatic, aromatic or heterocyclic acyl group or a carbamoyl group. The lower alkanoyl groups can be mentioned, such as for example, formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl.

R_a can also represent a lower alkoxy or cycloalkoxycarbonyl group, such as for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-cyclopropylethoxycarbonyl, isopropyloxycarbonyl, butyloxycarbonyl, tert- butyloxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, a benzoyl, toluolyl, naphthoyl, phthaloyl, mesyl, phenylacetyl, phenylpropionyl group, an aralkoxycarbonyl group, such as benzyloxycarbonyl.

The acyl groups can be substituted, for example, by a chlorine, bromine, iodine or fluorine atom. The following radicals can be mentioned: chloroacetyl, dichloroacetyl, trichloroacetyl, bromoacetyl or trifluoroacetyl.

R_a can also represent a lower aralkyl group such as benzyl, 4-methoxybenzyl, phenylethyl, trityl, 3,4-dimethoxybenzyl or benzhydryl.

R_a can also represent a haloalkyl group such as trichloroethyl.

R_a can also represent one of the following groups: chlorobenzoyl, para-nitrobenzoyl, para-tert-butylbenzoyl, phenoxyacetyl, caprylyl, n-decanoyl, acryloyl, trichloroethoxycarbonyl.

Ra can also represent a methyl carbamoyl, phenylcarbamoyl, naphthylcarbamoyl group, as well as the corresponding thiocarbamoyls.

The trityl group is preferred.

The above list is not limitative, it is obvious that other amine protective groups, in particular groups known in the chemistry of peptides, can also be used.

The protective group of the hydroxyl radicals which can be represented by R'_b and R'_c, can be chosen from the list below:

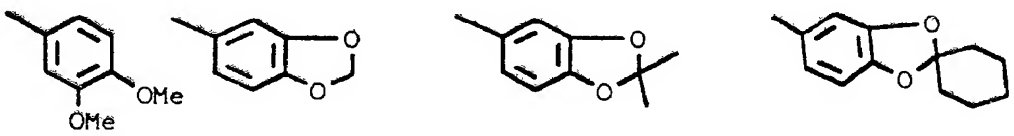
R'_b and R'_c can represent an acyl group, such as for example, formyl, acetyl, propionyl, chloroacetyl, bromoacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, benzoylformyl, p-nitrobenzoyl. The following groups can also be mentioned: ethoxy carbonyl, methoxycarbonyl, propoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl, tert-butoxycarbonyl, 1-cyclopropylethoxycarbonyl, tetrahydropyrannyl, tetrahydrothiopyrannyl, methoxytetrahydropyrannyl, trityl, benzyl, 4-methoxybenzyl, benzhydryl, trichloroethyl, 1-methyl-1-methoxyethyl, phthaloyl.

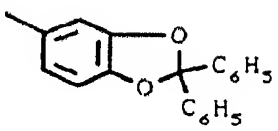
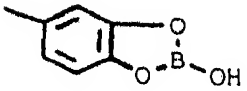
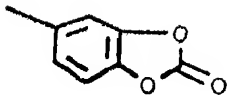
Other acyls can also be mentioned such as butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl and pivaloyl.

The following radicals can also be mentioned: phenylacetyl, phenylpropionyl, mesyl, chlorobenzoyl, para-nitrobenzoyl, para-tert-butylbenzoyl, caprylyl, acryloyl, methylcarbamoyl, phenylcarbamoyl, naphthylcarbamoyl.

The following radicals can also be mentioned: alkoxy alkoxy methyl, such as methoxy ethoxy methyl.

The OR'_b and OR'_c radicals can also form with the phenyl radical to which they are linked, the following values:



The methoxy ethoxy methyl group is preferred for substituents R'_b and R'_c.

In a method for implementing the process, a functional derivative of the product of formula (II) is reacted. This functional derivative can be for example, a halide, a symmetrical or mixed anhydride, an amide, an azide or an activated ester.

As an example of a mixed anhydride there can be mentioned, for example, that formed with isobutyl chloroformate and that formed with pivaloyl chloride and the carboxylic-sulphonic mixed anhydrides formed, for example, with the paratoluene sulphonyl chloride.

As an example of an activated ester, there can be mentioned the ester formed with 2,4-dinitrophenol and that formed with hydroxybenzothiazole.

As an example of the halide, there can be mentioned the chloride or bromide.

The anhydride can be formed in situ by action of N,N'-disubstituted carbodiimide, for example N,N-dicyclohexylcarbodiimide.

The acylation reaction preferably takes place in an organic solvent such as methylene chloride. However others solvents such as tetrahydrofuran, chloroform or dimethylformamide can be used.

When an acid halide is used and in a general manner when an acid halide molecule is released during the reaction, the reaction is preferably carried out in the presence of a base such as soda, potash, sodium or potassium carbonates and acid carbonates, sodium acetate, triethylamine, pyridine, morpholine or N-methylmorpholine.

The reaction temperature is, in general, lower or equal to ambient temperature.

Also a product of formula (II) can be reacted directly with a product of formula (III) in the presence of a carbodiimide such as diisopropylcarbodiimide. An example of such a preparation is given further on in the experimental part.

The action of the reagents capable of introducing the R_1 radical onto the product of formula (IV) is carried out in the following conditions:

When Hal represents, for example, a chlorine atom, a substitution of the chlorine atom by an iodine atom, in the presence of sodium iodide, can be carried out in situ or separately, then the desired reagent is added, either in the presence or not of an organic solvent such as acetonitrile or tetrahydrofuran. Examples of such reactions are described hereafter in the experimental part.

The desired reagent can also be reacted, in the presence of silver tetrafluoroborate, on the product of formula (IV) in which Hal represents a chlorine atom. An example of such a preparation is also to be found in the experimental part.

The isomerism of the products of formula (V) can be different to that of the products of formula (IV) used at the start. In the case where the Z isomer is isolated, this isomer can be converted into the E isomer according to usual methods, notably by the action of iodine.

According to the values of R_a, R'_b, R'_c, R_d and A", the products of formula (V) can or cannot constitute the products of formula (I).

The products of formula (V) constitute the products of formula (I) when R_a represents a hydrogen atom, when R'_b and R'_c do not represent a protective group of the hydroxyl radical that one wishes to eliminate, namely when R'_b and/or R'_c represent an acyl radical and when R_d and A" do not represent, among the easily cleavable ester groups, one of those that one would wish to eliminate.

In the other cases, the action on the product of formula (V) of one or more hydrolysis agents, hydrogenolysis agents or thiourea has the object of eliminating the R_a radical when

this represents a protective radical of the amino radical, of eliminating the R'_b and R'_c radicals when these represent a protective group of the hydroxyl radicals and/or of eliminating the R_d and A" radicals when these represent, among the easily cleavable ester groups one of those that one wishes to eliminate.

However, it is of course possible to eliminate R_a, R'_b and R'_c without touching substituents R_d and A" when these must be preserved. This is the case, for example, when A" represents an ester group that one wishes to preserve, such as a propionyloxymethyl group.

The nature of the reagents brought into play in such a case is well known to a man skilled in the art. Examples of such reactions are given further on in the experimental part.

For example, a description of the various elimination methods of the different protective groups will be found in the French Patent Application B.F. 2,499,995.

Given that the preferred protective groups used are: trityl for R_a, methoxy ethoxy methyl for R'_b and R'_c, diphenylmethyl for R_d and 4-methoxybenzyl or diphenylmethyl for A", trifluoroacetic acid without a solvent or in a solvent such as anisole or a mixture of solvents such as anisole/methylene chloride is preferably used. A salt is then obtained with trifluoroacetic acid. Return to the free base can be effected by the action of a base such as triethylamine carbonate.

The salification of the products can be carried out according to usual methods.

Salification can, for example, be obtained by the action of a mineral base such as sodium or potassium hydroxide, sodium or potassium carbonate or acid carbonate, on a product in acid form or on a solvate, for example, the ethanolic solvate or hydrate of this acid. Mineral acid salts such as trisodium phosphate can also be used. Organic acid salts can also be used.

As organic acid salts, there can be mentioned, for example, sodium salts of aliphatic, linear or branched,

saturated or unsaturated carboxylic acids with 1 to 18 carbon atoms and preferably with 2 to 10 carbon atoms. The aliphatic chains of these acids can be interrupted by one or more heteroatoms such as oxygen or sulphur or substituted by aryl radicals, such as, for example: phenyl, thienyl, furyl, by one or more hydroxyl radicals or by one or more halogen atoms such as fluorine, chlorine or bromine, preferably chlorine, by one or more carboxylic or lower alkoxycarbonyl radicals, preferably methoxycarbonyl, ethoxycarbonyl or propyloxycarbonyl, by one or more aryloxy radicals, preferably phenoxy.

Furthermore, as organic acids, sufficiently soluble aromatic acids can be used, such as, for example, substituted benzoic acids preferably substituted by lower alkyl radicals.

As examples of such organic acids, the following acids can be mentioned:
formic, acetic, acrylic, butyric, adipic, isobutyric, n-caproic, isocaproic, chloropropionic, crotonic, phenylacetic, 2-thienylacetic, 3-thienyl-acetic, 4-ethylphenylacetic, glutaric, the monoethylic ester of adipic acid, hexanoic, heptanoic, decanoic, oleic, stearic, palmitic, 3-hydroxy-propionic, 3-methoxypropionic, 3-methylthiobutyric, 4-chlorobutyric, 4-phenylbutyric, 3-phenoxybutyric, 4-ethylbenzoic, 1-propylbenzoic.

However sodiumacetate, sodium 2-ethyl hexanoate or sodim diethyl acetate are preferably used as sodium salts.

Salification can also be obtained by the action of an organic base such as triethylamine, diethylamine, trimethylamine, propylamine, N,N-dimethyl ethanolamine, tris[(hydroxymethyl)-amino] methane, methylamine, ethanolamine, pyridine, picoline, dicyclohexyl amine, morpholine and benzylamine.

It can also be obtained by the action of arginine, lysine, procaine, histidine, N-methyl glucamine. This salification is preferably carried out in a solvent or a mixture of solvents such as water, ethyl ether, methanol, ethanol or acetone.

The salts are obtained in amorphous or crystallized form

according to the reaction conditions employed.

Crystallized salts are prepared preferably by reacting free acids with one of the salts of the aliphatic carboxylic acids mentioned above, preferably, with sodium acetate.

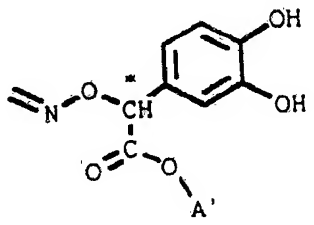
The salification of products by mineral or organic acids is carried out in the usual conditions.

The optional esterification of products is carried out in standard conditions. The operation is done, in general, by reacting the acid of formula (I) or a functional derivative with a derivative of formula:

Z - Re

in which Z represents a hydroxyl radical or a halogen atom such as chlorine, bromine, iodine and Re designates the ester group to be introduced, a non-exhaustive list of which groups is given above. In some cases, it can be advantageous to carry out an esterification on a product whose amine and/or reaction groups which are present on the oxyimino are blocked before removing the protective group of the amine and the reaction group which are present on the oxyimino.

The products of formula (I) comprise several asymmetrical carbons. In the cepheme nucleus, which comprises two asymmetrical carbons, the two carbon are in R configuration. Furthermore the radical present on the oxyimino function also comprises an asymmetrical carbon:



which can be in R or S form or in the form of an R, S mixture. The separation of the two diastereoisomers can be carried out by ways known to a man skilled in the art, for example, by chromatography.

The products of general formula (I) have a very good

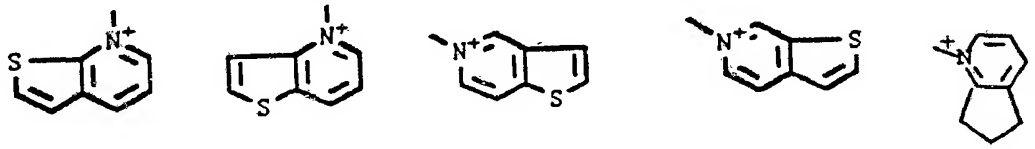
antibiotic activity on gram (+) bacteria such as staphylococcus, streptococcus and notably on penicillin-resistant staphylococcus. Their effectiveness on gram (-) bacteria notably on coliform bacteria, klebsiella, salmonella, proteus and pseudomonas, is particularly remarkable.

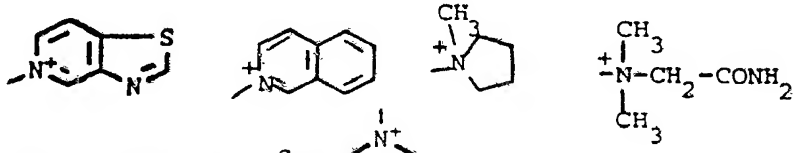
These properties render said products, as well as their salts of pharmaceutically acceptable acids, suitable to be used as medicaments in the treatment of affections caused by sensitive germs and notably in that of staphylococcis, such as staphylococcus septicemia, malignant staphylococcis of the face or skin, pyodermitis, septic or suppurating wounds, anthrax, phlegmons, erysipelas, acute primitive or post-influenza staphylococcis, bronchopneumonia, lung suppurations.

These products can also be used as medicaments in the treatment of colibacillosis and associated infections, in infections due to proteus, klebsiella and salmonella and in others affections caused by gram (-) bacteria.

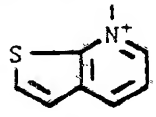
Therefore a subject of the present invention is also, as medicaments and notably antibiotic medicaments, the products of formula (I) as defined above as well as their salts with pharmaceutically acceptable acids.

More particularly a subject of the invention is as medicaments, the products of formula (I) as described above in which R_1 is chosen from the radicals:





preferably the radical:



Especially a subject of the invention is, as medicaments and notably antibiotic medicaments, the products described hereafter in the examples, namely:

- [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2- amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c] pyridinium in R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[(2- amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2- oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium in R or S form or in the form of an R, S mixtureand in the form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metal, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters and particularly in the S form,

- [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl] isoquinolinium in R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily clivables esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium in R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4 thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H pyridinium

in R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium in R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters.

The invention extends to pharmaceutical compositions containing, as active ingredient, at least one of the medicaments defined above.

These compositions can be administered by buccal, rectal, parenteral route, notably intramuscular or local route as a topical application on the skin and mucous membranes.

The products of formula (I) and notably those in which A represents a cleavable ester can be administered by oral route.

The pharmaceutical compositions according to the invention can be solid or liquid and be presented in the pharmaceutical forms currently used in human medicine, such as for example, plain or sugar-coated tablets, capsules, granules, suppositories, injectable preparations, ointments, creams, gels; they are prepared according to the usual methods. The active ingredient or ingredients can be incorporated with excipients usually employed in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents, preservatives.

These compositions can notably be presented in the form of a powder intended to be dissolved extemporaneously in an

appropriate vehicle, for example, apyrogenic sterile water.

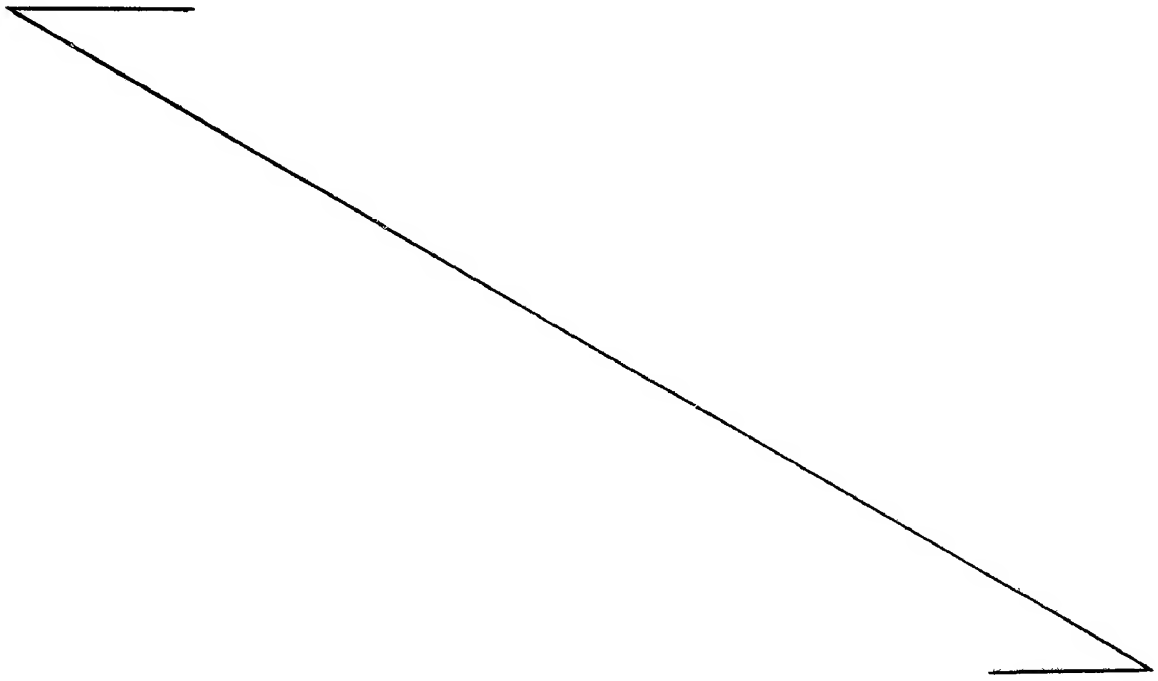
The dose administered is variable according to the affection treated, the subject in question, the administration route and the product used. It can be, for example, comprised between 0.250 g and 4 g per day, by oral route for an adult, for the product described in Example 1 or also comprised between 0.500 g and 1 g three times per day by intramuscular route.

The products of formula (I) can also be used as disinfectants for surgical instruments.

Finally a subject of the invention is, as new industrial products and notably as intermediate products necessary for the preparation of the products of formula (I) as defined above, the products of formula (IV) and the products of formula (V) in which R_a represents a protective group of the amino radical, formulae (IV) and (V) being as defined above.

The products of formula (II) are known from the literature, notably in the European Patent Application EP 0,238,061 or EP 0,266,060 or can be prepared according to usual methods.

The products of formula (III) are also known from the literature, notably in the British Patent Application GB 2,134,522 or the German Patent DE 3512225.



The following examples illustrate the invention without however limiting it.

EXAMPLE 1: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[(2-amino-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium trifluoroacetate tetrafluoroborate

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-diphenylmethyl-7-[[[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-ene-2-carboxylate.

0.372 cm^3 of diisopropylcarbodiimide in 1 cm^3 of methylene chloride is added to a mixture of 1.876 g of [[[3,4-bis-(2-methoxy-ethoxy)-methoxy]-phenyl]-(diphenyl-methoxy-carbonyl)-methoxy]-imino]-[2-(triphenyl-methyl-amino)-4-thiazolyl] acetic acid syn isomer, described in the European Patent EP 238061, 0.955 g of diphenylmethyl-7-amino-3- (3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]- oct-2-ene-2-carboxylate described in the German Patent DE 35 12 225 and 200 cm^3 of driedmethylene chloride.

Agitation takes place for 45 minutes then the solvent is evaporated off under reduced pressure and the residue is chromatographed on silica (eluant: methylene chloride 87.5 - ethyl acetate 12.5).

2.1 g of a yellow product is obtained (Rf = 0.42 thin layer chromatography, eluant: methylene chloride -ethyl acetate (8-2)).

Infrared

= C-NH	3402 cm^{-1}	
	1792 cm^{-1}	beta lactame
>=O	1731 cm^{-1}	ester
	1683 cm^{-1}	secondary amide
C=C	1594 cm^{-1}	
+	1584 cm^{-1}	
Aromatic	1525 cm^{-1}	
+	1517 cm^{-1}	
Secondary amide	1396 cm^{-1}	

Ultraviolet

1) In EtOH + 1 cm^3 $CHCl_2$

infl	217 nm	epsilon = 74300
infl	238 nm	epsilon = 35500
infl	271 nm	epsilon = 20800
infl	296 nm	epsilon = 16400

2) In EtOH + HCl 0.1 N

infl	217 nm	epsilon = 76400
infl	239 nm	epsilon = 28800
max	283 nm	epsilon = 26200
infl	271, 291 and 305 nm.	

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium tetrafluoroborate

A mixture of 55.9 mg of silver tetrafluoroborate, 38.8 mg of thieno-[2,3-b]- pyridine and 5 cm^3 of methylene chloride is treated with ultrasonics, then 136 mg of the product obtained in Stage A slightly diluted in methylene chloride is added and agitation takes place for 1 h 15.

After filtering and evaporating, the residue is taken up in ether, a solid is obtained which is washed with 3 times 3 cm^3 of ether and 207 mg of product is obtained which is purified by chromatography on silica (eluant: methylene chloride - methanol). The fractions are evaporated and 62 mg of product is obtained. Rf = 0.28 thin layer chromatography (eluant: methylene chloride - methanol (9:1)).

Ultraviolet

1) In EtOH

max	238 nm	epsilon = 368
infl	287 nm	epsilon = 168
max	300 nm	epsilon = 184

2) In EtOH, HCl 0.1 N

infl	236 nm	epsilon = 333
max	293 nm	epsilon = 209

STAGE C: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7- [[(2-amino-4-

thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2- oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium trifluoroacetate tetrafluoroborate

The following two solutions are mixed together at 0°C:
a) 0.180 g of product obtained in stage B, 4.3 cm^3 of methylene chloride and 0.86 cm^3 of anisole,
b) 8.6 cm^3 of trifluoroacetic acid and 4.3 cm^3 of methylene chloride, and agitation takes place for one hour at 0°C.

After evaporating and the product obtained is taken up in ether solidified. After filtering and washing with ether 100.6 mg of product is obtained which is placed in 3.3 cm^3 of a trifluoroacetic acid solution with 10% of anisole.

Agitation takes place for one hour at 0°C, followed by evaporating then precipitating the product in ether. After filtering and rinsing 87.9 mg of expected product is obtained.

EXAMPLE 2: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[(2-amino-4 thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium in the form of an internal salt

A mixture of 89.4 mg of the product obtained as in Example 1, 2.84 cm^3 of acetonitrile and 2.84 cm^3 of a 0.1N solution of triethylamine carbonate is eluted on an RP 18 silica column with a CH_3CN-H_2O (50-50) mixture. The useful fractions are lyophilized and 50.8 mg of expected product is obtained.

Infrared (Nujol)

Beta lactame	1770 cm^{-1}
Other C = O's	1675 cm^{-1}
	approx. 1598 cm^{-1}

Ultraviolet, in EtOH, HCl 0.1 N

max	240 nm	epsilon = 28600
max	290 nm	epsilon = 24000

EXAMPLE 3: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c] pyridinium

trifluoroacetate iodide

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-diphenylmethyl-7-[[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3-(3-iodo-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-ene-2-carboxylate.

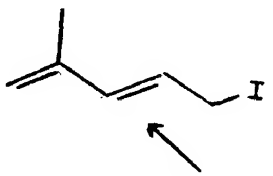
A mixture of 650 mg of product obtained in Stage A of Example 1, 19.1 cm^3 of acetone and 216.3 mg of sodium iodide is agitated for 2 hours at ambient temperature, the solvent is evaporated off then the residue is taken up in 26.5 cm^3 of ethyl acetate.

The solution is washed with 3 times 15 cm^3 of sodium thiosulphate then with 2 times 15 cm^3 of water.

After drying on magnesium sulphate, filtering, rinsing, evaporating, the residue is taken up in a methylene chloride - ethyl acetate (7-3) mixture, 5.3 g of silica is added, agitation takes place for 5 minutes follwed by filtering and rinsing.

445 mg of product is obtained after evaporation (Rf = 0.54 on thin layer chromatography, eluant methylene chloride - ethyl acetate (7-3)).

NMR in $CDCl_3$



ppm: 6.09 (dm J = 16)
6.12 (dm J = 16)

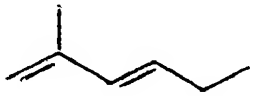
STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium iodide

A mixture of 445.2 mg of the product obtained in Stage A in the smallest possible quantity of dimethylsulphoxide and 48.2 mg of thiazolo-[4,5-c] pyridine is agitated for 5 hours, then the solvent is eliminated under reduced pressure.

The viscous residue is washed with 3 times 7 cm^3 of ether. 374.6 mg of a solid is obtained which is purified on silica (eluant: methylene chloride - methanol (92-8)).

24 mg of product having the Z isomer, 21.2 mg of an E+Z mixture and 154.3 mg of product having the E isomer are obtained. (Rf = 0.18 on thin layer chromatography, eluant: methylene chloride - methanol (9-1)).

NMR ($CDCl_3$)



6.50 ppm 1H

STAGE C: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium trifluoroacetate iodide

A mixture of the two following solutions is agitated for one hour at 0°C:

a) 238.6 mg of product obtained in Stage B, 5.7 cm^3 of methylene chloride and 1.14 cm^3 of anisole and

b) 11.4 cm^3 of trifluoroacetic acid in 5.7 cm^3 of methylene chloride.

The solvents are evaporated off then the product is precipitated in ether. After filtering and washing, 0.124 g of product is obtained which is mixed with 4.14 cm^3 of trifluoroacetic acid and 0.46 cm^3 of anisole. Agitation takes place for 40 minutes maintaining the temperature at 0°. After evaporating the product is then precipitated in ether. After filtering, rinsing with ether and drying 95.8 mg of expected product is obtained.

EXAMPLE 4: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium in the form of an internal salt

A solution of 95 mg of the product obtained in Example 3, 3.6 cm^3 of acetonitrile and 3.8 cm^3 of triethylamine carbonate

is passed through an RP18 silica column. The column is eluted with a mixture of acetonitrile-water (50-50). The useful fractions are lyophilized and 63.8 mg of expected product is obtained.

Ultraviolet, in EtOH, HCl 0.1 N

max 225 nm epsilon = 38500

max 286 nm epsilon = 23500

infl 274, 300 and 356 nm

Infrared (Nujol)

>= O	1770 cm^{-1}	Beta lactame
	1676 cm^{-1}	complex
Aromatic region	1626 cm^{-1}	
$COO^{\ominus}$	1596 cm^{-1}	
Secondary amide	1536 cm^{-1}	

EXAMPLE 5: [6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)-propenyl]-thieno-[3,2-b]-pyridinium trifluoroacetate tetrafluoroborate.

STAGE A: 6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[7-[[[3,4-bis-[(2-methoxyethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)-propenyl]-thieno-[3,2-b]-pyridinium tetrafluoroborate.

The operation is carried out as in Stage B of Example 1 starting with 1.2 g of the product prepared as indicated in Stage A of Example 1, 346 mg of silver fluoroborate in 44 cm^3 of methylene chloride and 0.24 cm^3 of thieno-[3,2-b]-pyridine and after chromatography on silica (eluant: methylene chloride - methanol 92-8 then 96-4) 337 mg of expected product is obtained.

NMR ($CDCl_3$ 300 Hz)

$-CH=\underline{CH}-CH_2-$: 6.23 (dm, J=16) delta E

$-CH=CH-\underline{CH_2}-$: 5.44 (m)

the CH's of the thienyl : 7.67 (d, resolved) 8.25 (d,resolved)

the CH's of the pyridine : 7.76 (m), 8.74 (d, resolved), 8.93 (d, resolved)

STAGE B: [6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[[[(2- amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)propenyl]-thieno-[3,2-b]-pyridinium trifluoroacetate tetrafluoroborate.

The operation is carried out as in Stage C of Example 1 starting with 316.1 mg of the product obtained above in Stage A, 1.51 cm^3 of anisole in 7.5 cm^3 of methylene chloride and 13.7 cm^3 of trifluoroacetic acid in 7.5 cm^3 of methylene chloride. 183 mg of product is obtained, to which another 6.3 cm^3 of trifluoroacetic acid with 10% anisole is added and agitation is continued for 1 hour at 0°C. The solvent is evaporated off, the residue is taken up in ether, the precipitate is filtered, washed with ether and dried under reduced pressure. 124.1 mg of expected product is collected.

NMR (DMSO)

$=N-O-\underline{CH}-CO_2H$	:	5.33 (s)
$-CH-S$	:	5.15 (d)
N		
$S-CH_2-$	:	3.49 (m) partially masked
$-CH=\underline{CH}-CH_2$	:	6.33 (dt, J=5 and 8) delta E
$-H=\underline{CH}-CH_2$		
H_7		5.72 (m)
$N^{\oplus}-CH_2$		
phenyl		
H_5 thiazole		6.57 to 7.07
mobile H		
H_6', H_3', H_2', H_7', H_5' of thienopyridine	:	8.04 to 9.36

EXAMPLE 6: [6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)-propenyl]-thieno-[3,2-b]-pyridinium trifluoroacetatetetrafluoroacetate.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-diphenylmethyl-7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-

thiazolyl]-acetyl]-amino]-3-(3-iodo-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-ene-2-carboxylate.

The operation is carried out as in Stage A of Example 3 using 3 g of the chlorinated product obtained in Stage A of Example 1 in 100 cm^3 of acetone and 1.0 g of sodium iodide. 3.3 g of iodinated derivative identical to that obtained in Example 3 is obtained which is used as it is in the following stage.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-4-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[3,2-b]-pyridinium iodide.

The operation is carried out as in Stage B of Example 3 using 3.3 g of the iodinated derivative prepared in Stage A, 1.5 cm^3 of thieno-[3,2-b]-pyridine and replacing the dimethylsulphoxide with methylene chloride. 1.08 g of expected product is obtained.

NMR

$-CH=CH-\underline{CH_2}-N^+$: 5.69 to 5.84 (m) 3H (+ H_7)

$-CH=\underline{CH}-CH_2-N^+$: 6.33 (dt), 6.46 (dt)

H of thienopyridine : 7.83 to 9.72

STAGE C: [6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)-propenyl]-thieno-[3,2-b]-pyridinium trifluoroacetate tetrafluoroacetate.

The following two solutions are mixed together at 0°C and agitated for one hour:

a) 55 cm^3 of trifluoroacetic acid, 5.5 cm^3 of anisole and 25 cm^3 of methylene chloride,

b) 1.19 g of the product obtained as in Stage B in 20 cm^3 of methylene chloride and the synthesis is continued as indicated in Stage C of Example 3. 0.62 g of expected product is obtained.

NMR (DMSO 400 Hz)

$=N-O-\underline{CH}(\gamma)-CO_2H$: 5.33 (s)

$-CH(N)-S-$: 5.15 (d, resolved)

$S-CH_2-$: 3.49 (m) partially masked

$-CH=\underline{CH}-CH_2$: 6.33 (dt, J=16 and 8) delta E

$-H=\underline{CH}-CH_2$ and $-\underline{CH}=CH-CH_2$: 5.72 (m)

phenyl H_5 thiazole : 6.57 to 7.01

mobile H

H of thienopyridine : 8.04 to 9.36

EXAMPLE 7: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-pyridinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl] pyridinium iodide.

The operation is carried out as in Stage B of Example 6 starting with 1.47 g of the iodinated derivative obtained as indicated in Stage A of Example 3 and 480 microlitres of pyridine. 0.640 g of expected product is obtained.

NMR ($CDCl_3$ 400 MHz)

$-CH=CH-\underline{CH_2}-N^{\oplus}$: 5.15 to 5.50

$-CH=\underline{CH}-CH_2-N^{\oplus}$: 6.5 (dt, resolved) delta E

H_2 and H_6 of pyridine : 9.10 (m)

H_3 and H_5 of pyridine : 7.87 (m)

H_4 of pyridine : 8.27 (t, resolved)

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2- oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-

[4,2,0]-oct-2-en-3-yl]-2-propenyl]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage C of Example 6 using 0.638 g of the derivative obtained in the preceding Stage and 0.314 g of expected product is obtained.

NMR

$=N-O-\underset{\gamma}{CH}-CO_2H$: 5.32 (s)

H_6 : 5.14 (d) and 5.17 (d)

H_7 : 5.77 (m)

H_5 thiazole : 6.87 (sl)

C-NH-CH : 9.55 (d) and 9.62 (d)

phenyl : 6.65 to 6.80

$-CH=CH-CH_2$: 7.01 (d, resolved)

$-CH=CH-CH_2$: 6.30 (dt) delta E

$-CH=CH-CH_2$ approx. 5.41

H in position 2 and 6 of pyridine : 9.05 (d)

H in position 3 and 5 of pyridine approx. 8.13 (d)

H in position 4 of pyridine : 8.64 (t)

EXAMPLE 8: [6R-[3(E), 6alpha, 7beta(Z)]]-6-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-c]-pyridinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-6-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-c]-pyridinium iodide.

The operation is carried out as in Stage B of Example 6 starting with 2.08 g of the iodinated derivative prepared as indicated in Stage A of Example 3 and 1 g of thieno-[2,3-c] pyridine. 0.98 g of expected product is obtained.

NMR 1) In EtOH:

Infl. 220 nm epsilon = 87500

max. 239 nm epsilon = 57000

Infl. 274 nm epsilon = 25500

max. 306 nm epsilon = 27000

1) In EtOH/HCl 0.1N:

Infl. 220 nm epsilon = 87800

Infl. 236 nm epsilon = 53600

max. 284 nm epsilon = 32600

max. 293 nm epsilon = 32500

Infl. 320 nm epsilon = 24000

STAGE B: 6R-[3(E), 6alpha, 7beta(Z)]-6-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-c]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage C of Example 6 using 0.966 g of the iodinated derivative obtained in the preceding Stage A and 0.487 g of expected product is obtained.

NMR

$=N-O-\underline{CH}-CO_2H$: 5.32 (s)

H_7 : 5.78 (m)

H_5 thiazole : 6.86 (sl)

phenyl : 6.65 to 6.80

H_6, H_7 thienopyridine : 7.94 (d), 8.81 (d)

H_4, H_5 thienopyridine : 8.53 (d), 8.78 (d)

H_2 thienopyridine : 9.91 (s)

$-\underline{CH}=CH-CH_2$: 7.08 (dl, J=15.5)

$-CH=\underline{CH}-CH_2$: 6.35 (m) delta E

$-CH-CH-\underline{CH_2}$: 5.47 (d)

EXAMPLE 9: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium trifluoroacetate iodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium iodide

The operation is carried out as in Stage B of Example 6 starting with 1.33 g of the iodinated derivative prepared as in Stage A of Example 3 and 0.585 cm^3 of cyclopentyl pyridine. 1.07 g of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium trifluoroacetate iodide.

The operation is carried out as in Stage C of Example 6 using 1.053 g of the product obtained in stage A and the expected product is obtained.

NMR (DMSO 300 MHz)

CH_2-N^+	5.32 (m) 3H
O-CH-	
Aromatic H's	
H_5 thiazole -CH-CH-CH_2	6.70 to 6.90
H_6	: 5.16 (d, resolved)
H_7	: 5.77 (m, d, resolved after exchange)
-S-CH_2	: 3.4 to 3.8(m)
-CH=CH-CH_2	: 6.23 (d, t) delta E
H of cyclopentyl	: 2.23-3.15-3.8
H of pyridine	: 7.2 (m), 8.42 (d), 8.76 (d)
Mobile H	: 9.01 to 9.62
-CH-CH-CH_2	: 5.47 (d)

EXAMPLE 10: [6R-[3(E), 6alpha, 7beta(Z)]]-2-amino-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium trifluoroacetate iodide

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-2-amino-5-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c] pyridinium iodide.

The operation is carried out as in Stage B of Example 6 starting with the iodinated derivative prepared as in Stage A of Example 3 (from 272 mg of the chlorinated derivative and 90 mg of sodium iodide) and 30 mg of amino thiazolo pyridine. 42 mg of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-2-amino-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-aza-bicyclo-[4,2,0]-oct-2-en-3-yl]-2- propenyl]-thiazolo-[4,5-c]-pyridinium trifluoroacetate iodide.

The operation is carried out as in Stage C of Example 3 using 130 mg of the product obtained as in Stage A and 11.5 mg of expected product is obtained.

NMR (DMSO 400 MHz)

H_5 thiazole ethylenic aromatics	6.64 to 7.41
H_6 $N^{\oplus}-CH_2-CH-$ O-CH-	5.05 to 5.35
H_7	: 5.67 (m), 5.76 (m)
$-CH=\underline{CH}-CH_2-$	: 6.29
H_6, H_7 of thiazolo pyridine	: 8.42 (d), 8.49 (d)
H_2 of thiazolo pyridine	: 8.99 (sl)
mobile protons	8.67 9 (m) 9.54 (m) 10.15

EXAMPLE 11: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[3,2-c]-pyridinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-

thiazolyl]-acetyl]-amino]-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

A suspension containing 3.75 g of [[(3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetic acid syn isomer, described in the European Patent EP 238061 and 1.81 g of methoxybenzyl-7-amino-3-(3-chloropropenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-2-carboxylate (prepared as indicated in the European Patent EP 0,333,154 in methylene chloride is cooled down to 0°C, and 0.920 g of N-(dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride is added. The solution obtained is kept under agitation at 0°C for 30 minutes. The organic phase is washed with an aqueous solution of sodium chloride, dried and the solvents are eliminated. After chromatographing the residue on silica (eluant: methylene chloride - ether 85-15) and solidification in isopropyl ether, 4.546 g of expected product is obtained.

NMR ($CDCl_3$ 400 MHz)

$CO_2-\underline{CH_2}-\varphi$: 5.10 to 5.32

$\varphi-O-\underline{CH_3}$: 3.80

<u>STAGE B</u>: [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3-(3-iodo-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

A mixture of the product obtained in stage A, 10 cm^3 of acetone and 341 mg of sodium iodide and approximately 10 mg of iodine is agitated for one hour at ambient temperature, the solvent is evaporated off then the residue is taken up in 80 cm^3 of methylene chloride. The organic phase is washed with an aqueous solution of sodium thiosulfate then with water. After drying, the solvents are eliminated and the residue is chromatographed on silica (eluant: methylene chloride - ethyl acetate 8-2) and 853 mg of expected product is obtained.

NMR ($CDCl_3$ 300MHz)

$-\underline{CH}=CH-CH_2$ aromatics $CH=C$	6.9 to 7.35

$-CH=\underline{CH}-CH_2$: 6.13 (d, t J=15 and 8) delta E

$-CH=CH-\underline{CH_2}$: 4.0 (d)

STAGE C: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxy-benzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[3,2-c] pyridinium iodide.

2.48 g of the iodinated derivative is dissolved in 10 cm^3 of methylene chloride and 1.2 g of thieno-[3,2-c] pyridine in solution in 2 cm^3 of methylene chloride is added and trituration takes place for 1 hour at ambient temperature. 70 cm^3 of ether is added, the precipitate is filtered, washed with ether and chromatographed on silica (eluant: methylene chloride - methanol 95-5) and 1.117 g of expected product is obtained.

STAGE D: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[3,2-c]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage C of Example 6 using 1.117 g of the product obtained in Stage C and 0.618 g of expected product is obtained.

NMR (DMSO 300 MHz)

$=N-O-\underline{CH}-CO_2H$: 5.33 (s)

H_6 : 5.18

H_7 : 5.79 (m)

$N-\underline{NH}-CH$: 9.56 (d), 9.64 (d)

$-\underline{CH}=CH-CH_2$: 7.07 (d, J=15.5) delta E

$-CH=\underline{CH}-CH_2$: 6.36 (m)

H of thienopyridine : 8 to 9.71

aromatics and H_5 thiazole : 6.70 to 6.78; 6.85 (s,1)

mobile H's : 12.56

EXAMPLE 12: [6R-[(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-

imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-isoquinolinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2- [(paramethoxybenzyl)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-isoquinolinium iodide.

The operation is carried out as in Stage B of Example 6 starting with 2.48 g of iodinated derivative prepared as in Stage B of Example 11 and 1.04 cm^3 of isoquinoline. 1.26 g of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-isoquinolinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage C of Example 6 using 1.26 g of the product obtained in Stage A and 0.673 g of expected product is obtained.

NMR (DMSO 300 MHz)

$=N-O-\underline{CH}(\gamma)-CO_2H$	: 5.32 (s)
H_6	: 5.17 (m)
H_7	: 5.77 (m)
S $-\underline{CH_2}$	: 3.07
$N-\underline{NH}-CH$	: 9.54 (d), 9.62 (d)
$-\underline{CH}=CH-CH_2$	: 7.10 delta E
$-CH=\underline{CH}-CH_2$	: 6.37 (m) delta E
$-CH=CH-\underline{CH_2}-$	: 5.53 (d)
H of isoquinoline	: 8.9 to 10.06
aromatics and H_5 thiazole	: 6.45 to 6.37 (3H); 6.85 (s) H
mobile H's	: 7.30 (2H); 9 (2H)

EXAMPLE 13: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2-methyl-1H-

imidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.

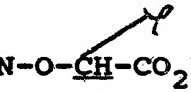
STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyl)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2-methyl-1H-imidazo-[4,5-c]-pyridinium iodide.

The operation is carried out as in Stage B of Example 6 starting with 1.92 g of the iodinated derivative prepared as in Stage B of Example 11 and 0.29 g of 2-methyl-1H-imidazo-[4,5-c]-pyridine. 1.055 g of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2-methyl-1H-imidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage C of Example 6 using 1.043 g of the product obtained in Stage A and 0.608 g of expected product is obtained.

NMR (DMSO 300 MHz)

	:	5.32 (s)
H_6	:	5.15 (d, resolved)
H_7	:	5.77 (m, d, resolved after exchange)
S-$\underline{CH}_2$	:	3.76 (d), 3.61 (masked)
N-$\underline{NH}$-CH	:	9.55 (d), 9.63 (d)
-$\underline{CH}$=CH-CH_2	:	6.95 (dl)
-CH=$\underline{CH}$-CH_2	:	6.35 (dt) delta E
-CH=CH-$\underline{CH}_2$-	:	5.42 (m)
CH_3 of imidazopyridine	:	2.70 (s)
H of pyridine	:	8.16 to 9.47
aromatics and H_5 thiazole	:	6.65 to 6.80 (m) 3H; 6.86 (s) 1H
mobile H's	:	7.34 (2H); 9.05 (m)

EXAMPLE 14: [6R-[3(E), 6alpha, 7beta(Z)]]-3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N,N-trimethyl-2-propen-1-aminium trifluoroacetate iodide

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxo-ethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N,N-trimethyl-2-propen-1-aminium iodide.

365 mg of the iodinated derivative as in Stage B of Example 11, 0.7 cm^3 of tetrahydrofuran and 220 microlitres of a solution of trimethylamine in ether (2.37 M/l) are agitated for 40 minutes at ambient temperature. 20 cm^3 of ether is added, the precipitate is separated and chromatographed on silica (eluant: methylene chloride - methanol 92-8), the residue is taken up in ether and after elimination of the solvent 276 mg of expected product is obtained.

Infra-Red

=C-NH	3404 cm^{-1} + associated
>=O	1791 cm^{-1} (beta lactame)
	1728 cm^{-1} esters
	1685 cm^{-1} amide
Conjugated system + amide II + aromatic	1632 cm^{-1} (shoulder)
	1613 cm^{-1}
	1596 cm^{-1}
	1586 cm^{-1}
	1525 cm^{-1}
	1517 cm^{-1}
	1496 cm^{-1}

Ultra-violet

1) In ethanol + 1 cm^3 CH_2Cl_2

infl.	219 nm	epsilon = 74000
max.	281 nm	epsilon = 23600
infl.	295 nm	epsilon = 22100
infl.	265, 276 nm	

2) In ethanol HCl 0.1n

infl.	219 nm	epsilon = 75000
max.	283 nm	epsilon = 30000

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-3-[7-[[(2-amino-4-

thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N,N-trimethyl-2-propen-1-aminium trifluoroacetate iodide.

247 mg of product obtained in Stage A with 2.5 cm^3 of trifluoroacetic acid with 10% of anisole is agitated for 1 hour at ambient temperature. 25 cm^3 of isopropyl ether is added, agitation is carried out for 10 minutes, the precipitate formed is isolated and dried under reduced pressure at 20°C for 24 hours. 128 mg of expected product is obtained.

NMR (DMSO 300 MHz)

$=N-O-\underset{\displaystyle Y}{CH}-CO_2H$	: 5.33 (s)
H_6	: 5.16 (d)
H_7	: 5.76 (d)
N-NH-CH	: 9.08 (d)
$-CH=CH-CH_2$	: 6.07 (m) delta E
$-CH=CH-CH_2$	: 7.04 (d)
$-CH=CH-CH_2-$	: 4.05 (d)
$^+N-(CH_3)_3$	: 2.99 (s), 3.03 (s)
aromatics and H_5 thiazole	: 6.70 to 6.9

EXAMPLE 15: [6R-[3(E), 6alpha, 7beta(Z)]]-[3-[7- [[(2-amino-4 thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2- hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N- (cyanomethyl)-N,N-dimethyl-2-propen-1-aminium] trifluoro-acetate iodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-[3-[7-[[[1-[3,4-bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N-(cyanomethyl)-N,N-dimethyl-2-propen-1-aminium] iodide.

The operation is carried out as in Stage A of Example 14 starting with 250 mg of the iodinated derivative and 250 cm^3 of a solution of dimethylamino acetonitrile in tetrahydrofuran (1-9). 172 mg of expected product is obtained.

NMR ($CDCl_3$ 400 MHz)

-CH=CH-CH_2: 6.05 (d,t) delta E

-CH=CH-CH_2- 5.05 to 5.35

CO_2-CH_2-

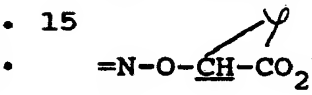
$^+$ N-CH_2-CN: 4.35 to 4.5

the CH_3's : 3.07 to 3.9

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-[3-[7-[[(2- amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2-hydroxy-2- oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N-(cyanomethyl)-N,N-dimethyl-2-propen-1-aminium]-trifluoroacetate iodide.

The operation is carried out as in Stage B of Example 14 starting with 172 mg of product prepared in Stage A. 72 mg of expected product is obtained.

NMR (DMSO 300 MHz)



: 5.33 (s)

H_6 : 5.20 (d)

H_7 : 5.82 (m)

N-NH-CH : 9.54 (d)

-CH=CH-CH_2 : 7.1 (d)

-CH=CH-CH_2 : 6.13 (m)

-CH=CH-CH_2- : 4.24 (d)

$\oplus$ N-$(CH_3)_2$: 3.19 (s)

$\oplus$ N-CH_2-CN : 4.8 (s)

aromatics and H_5 thiazole : 6.65 to 6.80 and 6.87

mobile H's : 7.79; 9.07

EXAMPLE 16: [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-[3-[7-[[(2-amino-4-thiazolyl)-[[1- (3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium]-trifluoroacetate iodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-[3-[7-[[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium] iodide.

350 mg of the iodinated derivative obtained as indicated in Stage B of Example 11 is mixed over one hour at 20°C with 1.6 cm^3 of acetonitrile and 27 mg of dimethylaminoacetamide. The solvents are eliminated under reduced pressure, the residue is chromatographed on silica (eluant: methylene chloride - methanol 97-3 then 92-8). 300 mg of expected product is collected.

NMR ($CDCl_3$ 300 MHz)

$-CH=\underline{CH}-CH_2-$	: 6.10 delta E
$-CH=CH-\underline{CH_2}-$	: 4.56
$-\underline{CH}=CH-CH_2$	
aromatic H's	6.85 to 7.37
NH_2	
the CH_3's	: 3.24 to 3.35
$\oplus N-\underline{CH_2}-C$	: 4.23 (m)

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]-N-(2-amino-2- oxoethyl)-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium] trifluoroacetate iodide.

The operation is carried out as in Stage B of Example 14 starting with 285 mg of product prepared as in Stage A above. 152 mg of expected product is obtained.

NMR (DMSO 300 MHz)

$=N-O-\underline{CH}(Y)-CO_2H$	: 5.34 (s)
H_6	: 5.19 (d)
H_7	: 5.85 (m)
the NH's	: 9.55 (d); 9.62 (d)
$-\underline{CH}=CH-CH_2$	: 7.03 (d, J=13.5) delta E)
$-CH=\underline{CH}-CH_2$	: 6.13 (m)
$-CH=CH-\underline{CH_2}-$	: 4.27 (d)
$\oplus N-(CH_3)_2$	: 3.19 (s)
$\oplus N-CH_2-$	: 4.01 (s)
aromatics and H_5 thiazole	: 6.72 to 6.8
mobile H's	

EXAMPLE 17: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-

oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl-pyrrolidinium trifluoroacetate iodide.

STAGE A: [6R-[3(E), 6alpha,7beta(Z)]]-[3-[7-[[[1-[3,4-bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium iodide.

357 mg of iodinated derivative obtained as indicated in Stage B of Example 11 is dissolved at 20°C in 7 cm^3 of ether and 1.3 cm^3 of methylene chloride. 130 microlitres of methyl-pyrrolidine and 5 cm^3 of ether are added, agitation is carried out for 10 minutes, the precipitate is isolated and dried at 20°C under reduced pressure. 300 mg of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium trifluoroacetate iodide.

The operation is carried out as in Stage B of Example 14 starting with 290 mg of product obtained in Stage A above. 150 mg of expected product is obtained.

NMR (DMSO 300 MHz)

$=N-O-\underline{CH}(Y)-CO_2H$	: 5.34 (s)
H_6	: 5.18 (d)
H_7	: 5.79 (m)
the -NH-CH's	: 9.52 (d); 9.61 (d)
$-\underline{CH}=CH-CH_2$	: 7.05 (d, J=15) delta E)
$-CH=\underline{CH}-CH_2$	: 6.17 (m) delta E
$-CH=CH-\underline{CH_2}-$	: 4.11 (d)
$\oplus N-CH_3$	: 2.99 (s)
pyrrolidine	: 2.10 (sl), 3.45 (sl)
aromatics and H_5 thiazole	: 6.65 to 6.85
mobile H's	: 9.10

EXAMPLE 18: **[6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[(2-amino-4-thiazolyl)-[[(R) 1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxo-ethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium trifluoroacetate hydroiodide.**

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-[[[(R)-1-[3,4-dihydroxy)-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

1.1 g of [[(R) (3,4-dihydroxyphenyl)-(diphenylmethoxy-carbonyl)-methoxy]-imino]-[2-(triphenylmethylamino)-4-thiazolyl] acetic acid syn isomer (prepared as indicated for isomer S in the European Patents EP 0,266,060 and 0,280,521 or in the German Patent DE 37 42 457 A1) in 11.36 cm^3 of methylene chloride. The solution obtained is cooled to -5°C, 403.4 mg of dicyclocarbodiimide is added, agitation is carried out for 40 minutes and 668 mg of p-methoxybenzyl-7-amino-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-2-carboxylate hydrochloride prepared as indicated in the European Patent EP 0,333,154. Agitation is carried out for 3 hours while allowing the temperature to return to ambient, the solvents are eliminated, the residue is chromatographed on silica (eluant: methylene chloride - ethyl acetate 9-1) and 712 mg of expected product is obtained.

NMR ($CDCl_3$ 300 MHz)

aromatics $COO-\underline{CH}-\varphi_2$ thiazole $=C-\underline{CH}=CH$	6.74 to 7.34
$-\underline{CH}=CH-CH_2$	: 6.25 (d, J=1) delta Z
$-CH=CH-\underline{CH_2}$	3.73 (dd) 3.92 (dd)
$CO_2-\underline{CH_2}-$	5.18 (s) 5.24

$-O\underline{CH_3}$: 3.81 (s)

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-[[[(R)-1-[3,4-[(dihydroxy)-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3(3-iodo-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

A mixture of 590 mg of product obtained in Stage A, 11.9 cm^3 of acetone and 216 mg of sodium iodide is agitated for 2 hours at ambient temperature, the solvent is evaporated then the residue is taken up in 5 cm^3 of methylene chloride. The solution is washed with 3 times 10 cm^3 of sodium thiosulphate then with 2 times 10 cm^3 of an aqueous solution of sodium chloride. After drying and crystallizing from ether, 456.6 mg of expected product is obtained.

NMR ($CDCl_3$ 400 MHz)

$=N-O-\underline{CH}(\varphi)-CO_2H$	: 5.86 (s)
H_6	: 4.85 (d)
H_7	: 5.74 (dd)
$S-\underline{CH_2}$	: 3.24
$C-\underline{NH}-CH$	: 8.10 (d)
$-CH=\underline{CH}-CH2$	: 6.00 (d, J=15.5 and 17.5) delta E
$-CH=CH-\underline{CH_2}-$	: 3.82 (d), 3.98 (d)
$-CO_2-\underline{CH_2}-$	: 5.24
$\varphi-O-CH_3$	: 3.80 (s)
aromatics and H_5 thiazole	: 6.68 to 7.40

STAGE C: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[[(R)-1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(p-methoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium iodide.

446 mg of iodinated derivative obtained in Stage B and 0.44 cm^3 of thieno pyridine are agitated and triturated for 2 hours at ambient temperature. Ether is added and the solid obtained is dried under reduced pressure for 24 hours. 442 mg of expected product is obtained.

NMR

$=N-O-CH-\varphi$: 5.55

$-CH=\underline{CH}-CH_2$: 6.30 (m) delta E

$-CH=CH-\underline{CH_2}$ 5.63 to 5.69

H_7

H of the thieno pyridine : 7.89 to 9.21

STAGE D: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[(2-amino-4-thiazolyl)-[[(R)1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxo-ethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium trifluoroacetate hydroiodide.

632 mg of product obtained as in Stage C in 6.32 cm^3 of a solution of trifluoroacetic acid with 10% anisole is agitated for one hour at ambient temperature. The mixture is cooled to +5°C, 65 cm^3 of isopropyl ether is added, followed by agitating for 10 minutes, filtering and drying under reduced pressure at ambient temperature for 16 hours. 403 mg of expected product is obtained.

NMR (DMSO 400 MHz)

$=N-O-\underline{CH}(\varphi)-CO_2H$: 5.31 (s)

H_6 : 5.18 (d)

H_7 : 5.77 (dd)

$S-\underline{CH_2}$: 3.73 (m)

$-\underline{CH}-CH-CH_2$: 7.15 (d, J=16) delta E

$-CH=\underline{CH}-CH_2$: 6.30 (d,t)

$-CH=CH-\underline{CH_2}-$: 5.68 (d)

H of the thieno pyridine : 7.88 to 9.23

aromatics, NH, H_5 thiazole : 6.70 to 7.35 (approx. 6H)

mobile H's : 7.31 to 9.61

EXAMPLE 19: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[(2-amino-4-thiazolyl)-[[(S)-1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxo-ethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium trifluoroacetate iodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-[[[(S)-1-[3,4-dihydroxy)-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

The operation is carried out as in Stage A of Example 18 starting with 678 mg of [[(S) (3,4-dihydroxyphenyl)-(diphenylmethoxycarbonyl)-methoxy]-imino]-[2-(triphenylmethylamino)-4-thiazolyl] acetic acid syn isomer prepared as indicated in the European Patents EP 0,266,060 and 0,280,521 or in the German Patent DE 37 32 457 A1 and 412 mg of p-methoxybenzyl hydrochloride of 7-amino-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-2-carboxylate. 590 mg of expected product is obtained.

NMR ($CDCl_3$ 400 MHz)

=N-O-CH-	: 5,89 (s)
-CH=CH-CH_2	5.81 (d,t)
	6.34 (d, J=12)

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-[[[(S)-1-[3,4-[(dihydroxy)-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3-(3-iodo-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

The operation is carried out as in Stage B of Example 18 using 850 mg of the product obtained in Stage A and 335 mg of sodium iodide. 595 mg of expected product is obtained.

Infra Red ($CHCl_3$)

OH	3548 cm^{-1}	
	3478 cm^{-1}	
NH	3401 cm^{-1}	
	3284 cm^{-1}	
>C=O	1772 cm^{-1}	beta lactame
	1725 cm^{-1}	ester
	1684 cm^{-1}	amide

	1614 cm^{-1}
aromatic	1601 cm^{-1}
heterocycle	1586 cm^{-1}
amide II	1529 cm^{-1}
C=C	1517 cm^{-1}
	1496 cm^{-1}

Ultra Violet

1) in dioxane:

infl. 224 nm E_1^1 = 566 epsilon = 69600
infl. 242 nm E_1^1 = 345
infl. 275 nm E_1^1 = 197
max. 282 nm E_1^1 = 201 epsilon = 24700
infl. 290 nm E_1^1 = 195
max. 314 nm E_1^1 = 218 epsilon = 26800

2) in dioxane/HCl 0.1N

max. 285 nm E_1^1 = 266 epsilon = 32700
infl. 304 nm E_1^1 = 244 epsilon = 30000
infl. 320 nm E_1^1 = 188 epsilon = 23100

STAGE C: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[[(S)-1-[3,4-bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino] [2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(p-methoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium iodide.

The operation is carried out as in Stage C of Example 18 using 430 mg of iodinated derivative obtained in Stage B and 470 mg of thieno pyridine. 438 mg of expected product is obtained.

Infra Red ($CHCl_3$)

NH/OH region complex

	1780 cm^{-1} beta lactame
-C=O	1725 cm^{-1} ester
	1684 cm^{-1} amide

	1613 cm^{-1}
	1600 cm^{-1}
aromatic	1586 cm^{-1}
heterocycle	1575 cm^{-1}
Amide II	1558 cm^{-1}
+ >C=C<	1525 cm^{-1}
	1516 cm^{-1}
	1496 cm^{-1}

STAGE D: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[(2-amino-4-thiazolyl)-[(S)-1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxo-ethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium trifluoroacetate iodide.

The operation is carried out as in Stage D of Example 18 using 400 mg of product obtained in Stage C. 275 mg of expected product is obtained.

NMR (DMSO 400 MHz)

$=N-O-\underline{CH}(\gamma)-CO_2H$	: 5.32 (s)
H_6	: 5.15
H_7	: 5.80 (dd, sl after exchange)
CO-NH-	: 9.55 (d)
C-NH-CH	: 9.55 (d)
$S-\underline{CH_2}$	: 3.51 (m)
$-\underline{CH}-CH-CH_2$	: 7.13 (d, J=16) delta E
$-CH=\underline{CH}-CH_2$	: 6.27 (d,t J=16 and 6)
$-CH=CH-\underline{CH_2}-$	: 5.67 (d, J=6)
H of the thieno pyridine	: 7.89 to 9.55
aromatics and H_5 thiazole	: 6.60 to 6.87 (m)

EXAMPLE 20: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1,2-dimethylimidazo-[4,5-c] pyridinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-

acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1,2-dimethylimidazo-[4,5-c]-pyridinium iodide.

1.08 g of product obtained as indicated in Stage B of Example 11 is agitated for one hour with 170 mg of 1,2-dimethyl-4-aza benzimidazole in 0.9 cm^3 of acetonitrile. 40 cm^3 of ether is added, the precipitate is filtered off, rinsed with ether and dried for 16 hours under reduced pressure. After chromatography on silica (eluant: methylene chloride - methanol 94-6), 306 mg of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1,2-dimethylimidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Example 14 Stage B starting with 297 mg of product obtained in Stage A. 155 mg of expected product is obtained.

NMR (DMSO 400 MHz)

$=N-O-\underset{\gamma}{CH}-CO_2H$	: 5.40 (sl)
and $CH=CH-\underline{CH_2}$	: 5.30 (s) 3H
H_6	: 5.13 (d)
H_7	: 5.75 (m)
$C-\underline{NH}-CH$	: 9.63 (d), 9.65 (d)
$-\underline{CH}-CH-CH_2$	: 6.98 (d, J=15.5) delta E
$-CH=\underline{CH}-CH_2$	: 6.30 (d,t)
the CH_3's	: 2.71 (s), 3.92 (s)
imidazopyridine	: 8.28 to 9.48
aromatics and H_5 thiazole	: 6.66 to 6.85
mobile H's	: 9.00, 9.08

EXAMPLE 21: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2,3-dimethylimidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis-

[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2,3-dimethylimidazo-[4,5-c] pyridinium iodide.

The operation is carried out as indicated in Stage A of Example 20 using 1.92 g of product obtained as in Stage B of Example 11 and 303 mg of 2,3-dimethyl-4-aza benzimidazole. 877 mg of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4 thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2,3-dimethylimidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage B of Example 14 starting with 865 mg of product obtained in Stage A. 488 mg of expected product is obtained.

NMR (DMSO 400 MHz)

$=N-O-\underline{CH}(\diagup)-CO_2H$	: 5.31 (s) 3H
and $CH=CH-\underline{CH_2}$	: 5.41 (l)
H_6	: 5.15 (d, resolved)
H_7	: 5.76
$C-\underline{NH}-CH$	: 9.53 (d), 9.60 (d)
$-\underline{CH}-CH-CH_2$	(d, J=15.5) delta E
$-CH=\underline{CH}-CH_2$	6.34 (d,t)
the CH_3's	: 2.75 (s), 3.94 (s)
imidazopyridine	: 8.18 to 9.58
aromatics and H_5 thiazole	: 6.65 to 6.86
mobile H's	: 7.31 to 9.60

EXAMPLE 22: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-quinolinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[1-[3,4-bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-

oxoethoxy]-imino] [2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-quinolinium iodide.

The operation is carried out as in Stage B of Example 6 starting with 2.50 g of iodinated derivative prepared as in Stage B of Example 11 and 0.63 g of quinoline. 2.40 g of expected product is obtained which is purified by chromatography on silica (eluant: methylene chloride - methanol 95-5).

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7- [[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2- hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-quinolinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage B of Example 14 using 1.65 g of the product obtained in Stage A and 0.94 g of expected product is obtained.

NMR (DMSO 400 MHz)

$=N-O-\underline{CH}(\gamma)-CO_2H$	: 5.31 (s)
H_6	: 5.14 (d)
H_7	: 5.75 (m)
$C-\underline{NH}-CH$	: 9.48 (d), 9.52 (d)
$-\underline{CH}-CH-CH_2$	: 6.97 (d, J=15) delta E
$-CH=CH-\underline{CH_2}$	: 5.89 (m)
H of the quinoline	: 8.07 to 9.59
aromatics and H_5 thiazole	: 6.64 to 6.77; 6.85 (s)
mobile H's	: 9.03 to 9.52

EXAMPLE 23: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-4-ethylthio pyridinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta (Z)]]-1-[3-[7-[[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-

thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-4-ethylthio pyridinium iodide.

The operation is carried out as in Stage B of Example 6 starting with 2.50 g of iodinated derivative prepared as in Stage B of Example 11 and 1 cm^3 of 4-ethylthio pyridine. 2.45 g of expected product is obtained which is purified by chromatography on silica (eluant: methylene chloride - methanol 95-5).

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-4-ethylthio pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage B of Example 14 using 1.54 g of the product obtained in Stage A and 0.807 g of expected product is obtained.

NMR (DMSO 400 MHz)

$=N-O-\underline{CH}-CO_2H$	: 5.32 (s)
H_6	: 5.16
H_7	: 5.77 (m)
$C-\underline{NH}-CH$	: 9.47 (d)
$-\underline{CH}-CH-CH_2-$	6.98 (d, J=16) delta E
$-CH=\underline{CH}-CH_2-$	6.26 (d,t)
H of the pyridine	: 7.97 to 8.69
aromatics and H_5 thiazole	: 6.67 to 6.78; 6.87 (s)
mobile H's	: 9.04 to 13.80

EXAMPLE 24: Preparations for injection were made of formula:

- Product of Example 2 ..... 500 mg
- sterile aqueous excipient sufficient quantity for ..... 5 cm^3

~~PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION~~

~~In vitro activity, method of dilutions in solid medium.~~

~~A series of dishes is prepared into which an equal quantity of sterile nutritive medium is divided, containing increasing quantities of the product to be studied, then each dish is seeded with several bacterial strains.~~

EXAMPLE 25: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 7-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] furo[2,3-b]pyridinium (R) or (S) or an (R+S) mixture,

Stage A: p-methoxy benzyl [6R-[3(E), 6alpha, 7beta(Z)]] 7-[[[(diphenylmethoxy carbonyl) [3,4-bis[(2-methoxy ethoxy) methoxy] phenyl] methoxy] imino] [2-[(triphenylmethyl) amino] 4-thiazolyl] acetyl] amino] 3-(3-chloro 1-propenyl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl-2-carboxylate.

A suspension containing 3.75 g of [[(diphenylmethoxy-carbonyl) [3,4-bis[(2-methoxy ethoxy) methoxy] phenyl] methoxy] imino] [2-[(triphenylmethyl) amino] 4-thiazolyl] acetic acid syn isomer (described in the European Patent EP 238061) and 1.81 g of p-methoxy benzyl 7-amino 3-(3-chloropropenyl) 8-oxo 5-thia 1-azabicyclo [4,2,0] oct-2-en-2-carboxylate (prepared as indicated in the European Patent EP 0 333 154) in dichloromethane is cooled down to 0°C, and 0.920 g of N-(dimethylaminopropyl) N'-ethyl carbodiimide hydrochloride is added. The solution obtained is kept at 0°C under agitation for 30 minutes. The organic phase is washed with an aqueous solution of sodium chloride, dried and the solvents are eliminated. After chromatographing the residue on silica (eluant: methylene chloride - ether 85-15) and concretion in isopropyl ether, 4.546 g of expected product is obtained.

NMR ($CDCl_3$ 400 MHz in ppm)

5.10 to 5.32: $CO_2-C\underline{H}_2-Ar$ (Ar: aromatic ring)

3.80: $Ar-O-C\underline{H}_3$

Stage B: p-methoxy benzyl [6R-[3(E), 6alpha, 7beta(Z)]] 7-[[[[(diphenylmethoxy carbonyl) [3,4-bis[(2-methoxy ethoxy) methoxy] phenyl] methoxy] imino] [2-[(triphenylmethyl) amino] 4-thiazolyl] acetyl] amino] 3-(3-iodo 1-propenyl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl-2-carboxylate.

A mixture of the product obtained in Stage A, 10 cm^3 of acetone and 341 mg of sodium iodide and approximately 10 mg of iodine is agitated for one hour at ambient temperature, the solvent is evaporated off then the residue is taken up in 80

cm^3 of dichloromethane. The organic phase is washed with an aqueous solution of sodium thiosulphate then with water. After drying, the solvents are eliminated, the residue is chromatographed on silica [eluant: dichloromethane - ethyl acetate (8-2)] and 853 mg of expected product is obtained.

NMR of the proton, ($CDCl_3$ 300MHz)

6.9 to 7.35: $-C\underline{H}=CH-CH_2-I$, Ar-$\underline{H}$

6.13 (d,t J=15 and 8): $-CH=C\underline{H}-CH_2-I$, E isomerism

4.0 (d): $-CH=CH-C\underline{H}_2-I$

Stage C: (±)(cis)(Z) 7-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] furo[2,3-b]pyridinium iodide.

1.928 g of the product prepared in Stage B, 0.365 g of furo[2,3-b]pyridine and 2 cm^3 of dichloromethane are agitated for two hours and 30 minutes, 40 cm^3 of sulphuric ether is added, the precipitate is isolated, rinsed with ether, dried and chromatographed on silica eluting with a dichloromethane - methanol (92-8) mixture; 0.5106 g of the expected product is collected. Rf = 0.38

NMR of the proton ($CDCl_3$, 400 MHz, in ppm)

3.22 (s), 3.29 (s) and 3.35 (s): $-O-CH_2-O-CH_2-CH_2-O-C\underline{H}_3$

3.79 (s): $Ar-OC\underline{H}_3$

3.10 to 3.9: $-S-C\underline{H}_2-C(CH=CH-)=C-$ and $-O-CH_2-O-C\underline{H}_2-C\underline{H}_2-O-CH_3$

5.00 (d) and 5.04 (d): $-CO-NH-CH(C=O)-C\underline{H}(N-)-S-$

5.15 to 5.35: $-O-C\underline{H}_2-O-CH_2-CH_2-O-CH_3$

5.32 (s): $-(C=O)-O-C\underline{H}_2-Ar$

5.79 (dd) and 5.85 (dd): $-CO-NH-C\underline{H}(C=O)-CH(N-)-S-$

5.99 (resolved): $Ar-C\underline{H}(C=O)-O-$

6.34 (m): $-CH=C\underline{H}-CH_2-N^+$

6.77 (resolved): $-S-C\underline{H}-C(C=N-)-N=$

6.84 to 7.45: Ar-$\underline{H}$, $-C\underline{H}=C\underline{H}-CH_2-N^+$ and the $\underline{H}$ in position 3 of the furo[2,3-b]pyridinium

7.87 (m): $\underline{H}$ in position 5 of the furo[2,3-b]pyridinium 8.03 (m): $\underline{H}$ in position 2 of the furo[2,3-b]pyridinium 8.35 (d): the $-N\underline{H}-$'s

8.66 (m): $\underline{H}$ in positions 4 and 6 of furo[2,3-b]pyridinium

Stage D: the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]

7-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] furo[2,3-b]-pyridinium (R) or (S) or an (R+S) mixture,

0.516 g of the product prepared in the previous stage and 5.1 cm^3 of a solution of trifluoroacetic acid with 10% anisole are agitated for one hour and fifteen minutes; then 30 cm^3 of sulphuric ether is added, agitation takes place again for one hour and 30 minutes, followed by filtering, rinsing and drying.

0.261 g of the desired product is collected.

NMR of the proton (DMSO, 400 MHz, in ppm)

3.50 to 3.78 (m): $-S-C\underline{H}_3-C(CH=CH-)=C-$

5.16 (d resolved): $-CO-NH-CH(C=O)-C\underline{H}(N-)-S-$

5.31 (s): $Ar-C\underline{H}(C=O)-O-$

5.58 (m): $-CH=CH-C\underline{H}_2-N^+$

5.77 (m): $-CO-NH-C\underline{H}(C=O)-CH(N-)-S-$

6.32 (m): $-CH=C\underline{H}-CH_2-N^+$

6.65 to 6.80 (m): aromatic H's of the (3,4-dihydroxy phenyl) (Ar-H)

6.85 (s): $-S-C\underline{H}-C(C=N-)-N=$

7.07 (d resolved): $-C\underline{H}=CH-CH_2-N^+$

7.52 (d): H in position 3 of the furo[2,3-b]pyridinium 7.98 (dd): H in position 5 of the furo[2,3-b]pyridinium 8.61 (d): H in position 2 of the furo[2,3-b]pyridinium 8.89 (dl) and 8.93 (d): H in positions 4 and 6 of the furo[2,3-b]pyridinium

7.31 (sl) (2 H) and 9.04 (m) (2 H): mobile H's

9.53 (d) and 9.61 (d): $-CO-N\underline{H}-CH(C=O)-CH(N-)-S-$

EXAMPLE 26: The internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 4-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] furo[3,2-b]-pyridinium (R) or (S) or an (R+S) mixture

By operating in a similar manner to that of Example 25, using furo[3,2-b]pyridine as quaternization agent, the desired product is obtained.

NMR of the proton (DMSO, 400 MHz, in ppm)

- S-CH$_2$-C(CH=CH-)=C- masked
5.14 (d resolved): -CO-NH-CH(C=O)-CH(N-)-S-
5.32 (s): Ar-CH(C=O)-O-
5.61 (m): -CH=CH-CH$_2$-N$^+$
5.76 (m): -CO-NH-CH(C=O)-CH(N-)-S-
6.30 (m): -CH=CH-CH$_2$-N$^+$ E isomer
6.6 to 6.78 (m): Ar-H
6.86 (s): -S-CH-C(C=N-)-N=
7.02 (d resolved): -CH=CH-CH$_2$-N$^+$
7.78 (sl): H in position 3 of the furo[3,2-b]pyridinium 8.06 (dd): H in position 6 of the furo[3,2-b]pyridinium 8.92 (d): H in position 2 of the furo[3,2-b]pyridinium 8.97 (d) to 9.04 (m): H in positions 5 and 7 of the furo[3,2-b]pyridinium
9.0 (m): mobile H's
9.48 (d) and 9.56 (d): -CO-NH-CH(C=O)-CH(N-)-S-

EXAMPLE 27: the internal salt of (S)(cis)(Z) 7-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabi-cyclo[4,2,0] oct-2-3-yl] 2(E)-propenyl] thieno[2,3-b] pyridinium

By operating in a similar manner to that of Example 25, using as starting product [[(S)-(diphenylmethoxycarbonyl) [3,4-bis[(2-methoxy ethoxy) methoxy] phenyl] methoxy] imino] [2-[(triphenylmethyl) amino] 4-thiazolyl] acetic acid syn isomer (described in European Patents EP 0266060 and 0280521) and thieno[2,3-b]pyridine as quaternization agent, the desired product is obtained.

Rf= 0.5 [thin layer chromatography (TLC); eluant: acetone - water (4-1)]

Alpha$_D$ = -11.5° [concentration (c) = 0.. in DMSO],

NMR of the proton (DMSO, 400 MHz, in ppm)

3.51 (m): -S-CH$_2$-C(CH=CH-)=C-
5.15 (d J=5): -CO-NH-CH(C=O)-CH(N-)-S-
5.32 (s): Ar-CH(C=O)-O-
5.67 (d, J=6): -CH=CH-CH$_2$-N$^+$
5.8 (dd, sl after exchange): -CO-NH-CH(C=O)-CH(N-)-S-
6.27 (dt J=16 and 6): -CH=CH-CH$_2$-N$^+$ E isomer
6.6 to 6.87 (m): Ar-H and-S-CH-C(C=N-)-N=

7.13 (d J=6): -CH=CH-CH_2-N^+

7.89 (d): H in position 3 of the thieno[2,3-b]pyridinium 8.15 (dd): H in position 5 of the thieno[2,3-b]pyridinium 8.28 (d): H in position 2 of the thieno[2,3-b]pyridinium 9.08 (d): H in position 4 of the thieno[2,3-b]pyridinium 9.22 (d): H in position 6 of the thieno[2,3-b]pyridinium 9.55 (d): -CO-NH-CH(C=O)-CH(N-)-S-

EXAMPLE 28: the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-methoxy pyridinium (R) or (S) or an (R+S) mixture,

By operating in a similar manner to that of Example 25, using 4-methoxy pyridine as quaternization agent, the desired product is obtained.

NMR of the proton (DMSO, 400 MHz, in ppm)

3.72 (AB): -S-CH_2-C(CH=CH-)=C-

4.10 (s): Ar-O-CH_3

5.15 (d): -CO-NH-CH(C=O)-CH(N-)-S-

5.22 (l): -CH=CH-CH_2-N^+

5.32 (s): Ar-CH(C=O)-O-

5.77 (m): -CO-NH-CH(C=O)-CH(N-)-S-

6.25 (m): -CH=CH-CH_2-N^+ E isomer

6.68 (dd), 6.74 (m) (2H) and 6.86 (s) (1H)=: Ar-H and -S-CH-C(C=N-)-N=

6.95 (d J=15.5): -CH=CH-CH_2-N^+

7.33: NH_2

7.66 (d) and 8.83 (m): aromatic H's of 4-MeO pyridinium

9.0 (l), 9.5 (d) and 9.62 (d): mobile H's

EXAMPLE 29: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-(methylthio) pyridinium (R+S),

By operating in a similar manner to that of Example 25, using 4-(methylthio) pyridine as quaternization agent, the desired product is obtained.

NMR of the proton (DMSO, 300 MHz, in ppm)

2.72 (s): Ar-S-C<u>H</u>$_3$

5.15 (d) and 5.18 (d): -CO-NH-CH(C=O)-C<u>H</u>(N-)-S-

5.22 (dl): -CH=CH-C<u>H</u>$_2$-N$^+$

5.32 (s): Ar-C<u>H</u>(C=O)-O-

5.77 (m, d resolved after exchange): -CO-NH-C<u>H</u>(C=O)-CH(N-)-S-

6.26 (m): -CH=C<u>H</u>-CH$_2$-N$^+$ E isomer

6.65 (dd) to 6.87 (m) (4 H)=: Ar-<u>H</u> and-S-C<u>H</u>-C(C=N-)-N=

6.99 (d J=15 Hz): -C<u>H</u>=CH-CH$_2$-N$^+$

7.96 (d) and 8.70 (d): aromatic <u>H</u>'s of 4-Mes pyridinium

9.55 (d) and 9.62 (d): -CO-N<u>H</u>-CH(C=O)-CH(N-)-S-

7.32 (m) and 9.06 (m): mobile <u>H</u>'s

<u>EXAMPLE 30</u>: the internal salt of [6R-[3(E), 6alpha, 7beta [Z-(R*)]]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-(methylthio) pyridinium,

The product obtained in Example 29 is purified by HPLC on a Microbondapack C_{18-300} (registered trademark) column of 10 microns and 0.019 m in diameter eluting with acetonitrile with 0.025% trifluoroacetic acid and in this way leads to the (R) and (S) isomers (See following example).

NMR of the proton (DMSO, 300 MHz, in ppm)

2.71 (s): Ar-S-C<u>H</u>$_3$

3.54 (d) and 3.79 (d): -S-C<u>H</u>$_2$-C(CH=CH-)=C-

5.17 (d): -CO-NH-CH(C=O)-C<u>H</u>(N-)-S-

5.22 (l): -CH=CH-C<u>H</u>$_2$-N$^+$

5.32 (s): Ar-C<u>H</u>(C=O)-O-

5.77 (d, d): -CO-NH-C<u>H</u>(C=O)-CH(N-)-S-

6.27 (m): -CH=C<u>H</u>-CH$_2$-N$^+$ E isomer

6.72 (d): <u>H</u> in position 5 of the (3,4-dihydroxy phenyl)

6.74 (s): -S-C<u>H</u>-C(C=N-)-N=

6.73 (d): <u>H</u> in position 6 of the (3,4-dihydroxy phenyl)

6,86 (d): <u>H</u> in position 2 of the (3,4-dihydroxy phenyl)

6.98 (d J=15,5 Hz): -C<u>H</u>=CH-CH$_2$-N$^+$

7.30 (l): -N<u>H</u>$_2$

7.96 (d) and 8.71 (d): aromatic <u>H</u>'s of 4-MeS pyridinium

9.62 (d): -CO-N<u>H</u>-CH(C=O)-CH(N-)-S-

9.00 and 9.09: mobile <u>H</u>'s

EXAMPLE 31: the internal salt of [6R-[3(E), 6alpha, 7beta [Z-(S*)]]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-(methylthio) pyridinium,

NMR of the proton (DMSO, 300 MHz, in ppm)

2.72 (s): Ar-S-C<u>H</u>$_3$

3.54 [AB]: -S-C<u>H</u>$_2$-C(CH=CH-)=C-

5.14 (d): -CO-NH-CH(C=O)-C<u>H</u>(N-)-S-

5.22 (dl): -CH=CH-C<u>H</u>$_2$-N$^+$

5.32 (s): Ar-C<u>H</u>(C=O)-O-

5.79 (dd): -CO-NH-C<u>H</u>(C=O)-CH(N-)-S-

6.24 (dt): -CH=C<u>H</u>-CH$_2$-N$^+$ E isomer

6.65 to 6.78 (m) (3H) and 6.87 (1H): Ar-<u>H</u> and-S-C<u>H</u>(C=N-)-N=

6.97 (d): -C<u>H</u>=CH-CH$_2$-N$^+$

7.30 (l): -N<u>H</u>$_2$

7.96 (d) and 8.70 (d): aromatic <u>H</u>'s of 4-MeS pyridinium

9.55 (d): -CO-N<u>H</u>-CH(C=O)-CH(N-)-S-

9.04 and 9.08: mobile <u>H</u>'s

EXAMPLE 32: The internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 2-(methylthio) pyridinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

2.87 (s): Ar-S-C<u>H</u>$_3$

5.16 (d, resolved): -CO-NH-CH(C=O)-C<u>H</u>(N-)-S-

5.78 (d, resolved after exchange): -CO-NH-C<u>H</u>(C=O)-CH(N-)-S-

6.13: -CH=C<u>H</u>-CH$_2$-N$^+$ E isomer

6.65 to 6.80: Ar-<u>H</u>

6.85: -S-C<u>H</u>(C=N-)-N=

6.85 (d resolved): -C<u>H</u>=CH-CH$_2$-N$^+$

7.32 and 9.05: -O<u>H</u>

7.84 (t) and 8.44 (t): aromatic <u>H</u>'s in position 3 and 4 of the 2-MeS pyridinium

8.04 (d): aromatic <u>H</u> in position 5 of the 2-MeS pyridinium

8.97 (d): aromatic <u>H</u> in position 2 of the 2-MeS pyridinium

9.57 (d resolved): -CO-N<u>H</u>-CH(C=O)-CH(N-)-S-

EXAMPLE 33: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-(amino-carbonyl) pyridinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

3.50 to 3.75 (m): $-S-C\underline{H}_2-C(CH=CH-)=C-$

5.17 (d resolved): $-CO-NH-CH(C=O)-C\underline{H}(N-)-S-$

5.32 (s): $Ar-C\underline{H}(C=O)-O-$

5.44 (m): $-CH=CH-C\underline{H}_2-N^+$

5.77 (m): $-CO-NH-C\underline{H}(C=O)-CH(N-)-S-$

6.29 (m): $-CH=C\underline{H}-CH_2-N^+$ E isomer

6.66 to 6.78 (m) (3 H): $Ar-\underline{H}$

6.86 (s): $-S-C\underline{H}(C=N-)-N=$

7.06 (d, J=15.5): $-C\underline{H}=CH-CH_2-N^+$

8.44 (d): $\underline{H}$ in positions 3 and 5 of the pyridinium ring

8.67 (s) and 8.25 (s): $(C=O)-N\underline{H}_2$ slightly mobile

9.20 (d): $\underline{H}$ in positions 2 and 6 of the pyridinium ring

9.47 (d) and 9.54 (d): $-CO-N\underline{H}-CH(C=O)-CH(N-)-S-$

8.94 (m) (2 H) 7.24 (m) (2 H) and 12.85 (shoulder): mobile $\underline{H}$'s

EXAMPLE 34: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 3-(amino-carbonyl) pyridinium (R) or (S) or an (R+S) mixtureNMR of the proton (DMSO, 300 MHz, in ppm)

3.50 to 3.80 (m): $-S-C\underline{H}_2(CH=CH-)=C-$ masked

5.17 (d resolved): $-CO-NH-CH(C=O)-C\underline{H}(N-)-S-$

5.32 (s): $Ar-C\underline{H}(C=O)-O-$

5.44 (m): $-CH=CH-C\underline{H}_2-N^+$

5.77 (m): $-CO-NH-C\underline{H}(C=O)-CH(N-)-S-$

6.30 (m): $-CH=C\underline{H}-CH_2-N^+$ E isomer

6.64 to 6.90 (m) (4 H): $Ar-\underline{H}$ and $-S-C\underline{H}(C=N-)-N=$

7.08 (d J=15): $-C\underline{H}=CH-CH_2-N^+$

7.29 (3 H): $=C-N\underline{H}_2$

8.29 (t): $\underline{H}$ in position 5 of the pyridinium ring

8.36 (d): $\underline{H}$ in position 4 of the pyridinium ring

9.17 (d): $\underline{H}$ in position 6 of the pyridinium ring

9.47 (d): H in position 2 of the pyridinium ring
9.54 (d) and 9.62: -CO-NH-CH(C=O)-CH(N-)-S-
8.20 (s) and 8.61 (s): slightly mobile H's9.02: mobile H's

EXAMPLE 35: The internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 6-amino 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] quinolinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 400 MHz, in ppm)
5.13: -CO-NH-CH(C=O)-CH(N-)-S-
5.31 (d resolved): Ar-CH(C=O)-O-
5.65 to 5.80: $-CH=CH-CH_2-N^+$ and -CO-NH-CH(C=O)-CH(N-)-S-
6.32 (m): $-CH=CH-CH_2-N^+$ E isomer
6.65 to 7.0 (m) (5 H): Ar-H, -S-CH-C(C=N-)-N= and $-CH=CH-CH_2-N^+$
7.56 (d resolved): H in position 7 of the quinolinium ring
7.88 (m): H in position 3 of the quinolinium ring
8.19 (m): H in position 8 of the quinolinium ring
8.80 (d): H in position 4 of the quinolinium ring
9.0 (s):
9.53 (d) and 9.61 (d): -CO-NH-CH(C=O)-CH(N-)-S-

EXAMPLE 36: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 3-amino 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] quinolinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)
5.14: -CO-NH-CH(C=O)-CH(N-)-S-
5.31 (s) and 5.32 (s): Ar-CH(C=O)-O-
5.60 to 5.85 (m): $-CH=CH-CH_2-N^+$ and -CO-NH-CH(C=O)-CH(N-)-S-
6.33 (m): $-CH=CH-CH_2-N^+$ E isomer
6.6 to 6.8 (m): Ar-H,
6.86 (s): -S-CH-C(C=N-)-N=
6.98 (d resolved): $-CH=CH-CH_2-N^+$
7.76 (m) (2 H), 8.1 (m) (1 H) and 8.25 (m) (1 H): H in positions 5, 6, 7 and 8 of the quinolinium ring
8.03 (d): H in position 4 of the quinolinium ring
8.87 (s1): H in position 2 of the quinolinium ring

9.09 (m): mobile H's

9.53 (d) and 9.61 (d): -CO-NH-CH(C=O)-CH(N-)-S-

EXAMPLE 37: the internal salt of [6R-[3 (E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 3-methyl quinolinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

2.66 (s): $-CH_3$ in position 3 of the quinolinium ring

3,50 (masked) and 3.75 (d): $-S-CH_2(CH=CH-)=C-$

5.13 resolved: -CO-NH-CH(C=O)-CH(N-)-S-

5.31 (s): Ar-CH(C=O)-O-

5.78 (m): -CO-NH-CH(C=O)-CH(N-)-S-

5.85 (m): $-CH=CH-CH_2-N^+$

6.36 (m): $-CH=CH-CH_2-N^+$ E isomer

6.62 to 6.8 (m) (3 H): Ar-H

6.85 (s): -S-CH-C(C=N-)-N=

7.00 (d resolved): $-CH=CH-CH_2-N^+$

8.01 (t) and 8.19 (t): H in position 6 and 7 of the quinolinium ring

8.38 (d) and 8.50 (d): H in position 5 and 8 of the quinolinium ring

9.14 (sl) and 9.54 (sl): H in position 2 and 4 of the quinolinium ring

9.04 (m): mobile H's

9.53 (d) and 9.59 (d): -CO-NH-CH(C=O)-CH(N-)-S-

EXAMPLE 38: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-methyl quinolinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

3.02 (s): $-CH_3$ in position 4 of the quinolinium ring

3.45 to 3.80 (m): $-S-CH_2-C(CH=CH-)=C-$

5.13 (d resolved): -CO-NH-CH(C=O)-CH(N-)-S-

5.31 (s): Ar-CH(C=O)-O-

5.75 (d, resolved after exchange): -CO-NH-CH(C=O)-CH(N-)-S-

5.80 (m): $-CH=CH-CH_2-N^+$

6.37 (m): -CH=C<u>H</u>-CH_2-N^+ E isomer
approximately 6.70 (m) (3 H): Ar-<u>H</u>
6.85 (s): -S-C<u>H</u>-C(C=N-)-N=
6.96 (d resolved j=16Hz): -C<u>H</u>=CH-CH_2-N^+
8.06 (t) and 8.25 (t): <u>H</u> in position 6 and 7 of the quinolinium ring
8.11 (d): <u>H</u> in position 3 of the quinolinium ring
8.50 (2d): <u>H</u> in position 5 and 8 of the quinolinium ring
9.43 (d): <u>H</u> in position 2 of the quinolinium ring
7.30 (sl and 9.03 (sl): mobile <u>H</u>'s (-$N\underline{H}_2$ and -O<u>H</u>)
9.51 (d) and 9.59 (d): -CO-N<u>H</u>-CH(C=O)-CH(N-)-S-

<u>EXAMPLE 39</u>: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 6-methyl quinolinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)
2.62 (s). -$C\underline{H}_3$ in position 4 of the quinoleinium ring
3.50 (masked) and 3.74 (d): -S-$C\underline{H}_2$-C(CH=CH-)=C-
5.13 (d resolved): -CO-NH-CH(C=O)-C<u>H</u>(N-)-S-
5.31 (s): Ar-C<u>H</u>(C=O)-O-
5.76 (d, resolved after exchange): -CO-NH-C<u>H</u>(C=O)-CH(N-)-S-
5.86 (m): -CH=CH-$C\underline{H}_2$-N^+
6.35 (m): -CH=C<u>H</u>-CH_2-N^+ E isomer
6.85 (s resolved): -S-C<u>H</u>-C(C=N-)-N=
6.94 (d resolved j=16Hz): -C<u>H</u>=CH-CH_2-N^+
8.10 to 8.45 (m) (4 H): <u>H</u> in position 3, 5, 7 and 8 of the quinolinium ring
9.21 (d) (1 H): <u>H</u> in position 4 of the quinolinium ring
9.50 (d): <u>H</u> in position 2 of the quinolinium ring
9.03 (m): mobile <u>H</u>'s
9.50 (d) and 9.60 (d): -CO-N<u>H</u>-CH(C=O)-CH(N-)-S-

<u>EXAMPLE 40</u>: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 6-chloro quinolinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

3.60 (masked) and 3.75 (d): -S-CH_2(CH=CH-)=C-
5.14: -CO-NH-CH(C=O)-CH(N-)-S-
5.31 (s): Ar-CH(C=O)-O-
5.76 (m): -CO-NH-CH(C=O)-CH(N-)-S-
5.88 (m): -CH=CH-CH_2-N^+
6.34 (m): -CH=CH-CH_2-N^+ E isomer
6.85 (s): -S-CH-C(C=N-)-N=
6.96 (d resolved): -CH=CH-CH_2-N^+
6.62 to 6.80 (m) (3 H): Ar-H
8.29 (m) and 8.59 (dd): H in positions 3, 7 and 8 of the quinolinium ring
8.69 (d): H in position 5 of the quinolinium ring
9.25 (d): H in position 4 of the quinolinium ring
9.59 (d): H in position 2 of the quinoleinium ring
9.04 (m): mobile H's
9.52 (d) and 9.60 (d): -CO-NH-CH(C=O)-CH(N-)-S-

EXAMPLE 41: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 6-methoxy quinolinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 400 MHz, in ppm)
3.45 to 3.75 (m): -S-CH_2-C(CH=CH-)=C-
4.00 (s): -OCH_3 in position 6 of the quinolinium ring
5.12 (d resolved): -CO-NH-CH(C=O)-CH(N-)-S-
5.31 (s): Ar-CH(C=O)-O-
5.74 (dd resolved): -CO-NH-CH(C=O)-CH(N-)-S-
5.84 (m): -CH=CH-CH_2-N^+
6.35 (m): -CH=CH-CH_2-N^+ E isomer
6.65 to 6.80 (m): Ar-H
6.85 (s): -S-CH-C(C=N-)-N=
6.93 (d resolved J=16Hz): -CH=CH-CH_2-N^+
7.89 (dd): H in position 7 of the quinolinium ring
7.90 (sl): H in position 5 of the quinolinium ring
8.15 (dd): H in position 3 of the quinolinium ring
8.46 (dd): H in position 4 of the quinolinium ring
9.13 (d): H in position 8 of the quinolinium ring
9.37 (d): H in position 2 of the quinolinium ring

7.27 (m) (2 H) and 8.94 (m) (2 H): mobile H's
9.45 (d) and 9.52 (d): -CO-NH-CH(C=O)-CH(N-)-S

EXAMPLE 42: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 3-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] thiazolium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 400 MHz, in ppm)
3.40 3.80 (m): $-S-CH_2-C(CH=CH-)=C-$
5.16 (d resolved): -CO-NH-CH(C=O)-CH(N-)-S-
5.33 (m) (3 H): Ar-CH(C=O)-O- and $-CH=CH-CH_2-N^+$
5.77 (m): -CO-NH-CH(C=O)-CH(N-)-S-
6.26 (m): $-CH=CH-CH_2-N^+$ E isomer
6.65 to 6.77 (m): Ar-H
6.87 (s): -S-CH-C(C=N-)-N=
6.97 (d resolved): $-CH=CH-CH_2-N^+$
7.30 (s) (2 H): mobile H's
8.36 (s) and 8.52 (s): H in position 4 and 5 of the thiazolium ring9.00 (s), 9.08 (s), 9.09 (s) and 9.64 (s): mobile 2 H's
9.54 (d) and 9.62 (d): -CO-NH-CH(C=O)-CH(N-)-S-
10.21 (s): H in position 2 of the thiazolium ring

EXAMPLE 43: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 3-methyl imidazolium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 400 MHz, in ppm)
3.50 to 3.80: $-S-CH_2-C(CH=CH-)=C-$
3.86 (s): $-CH_3$ in position 3 of the imidazolium ring
4.97 (d): $-CH=CH-CH_2-N^+$
5.16 (d resolved): -CO-NH-CH (C=O)-CH(N-)-S-
5.33 (s): Ar-CH(C=O)-O-
5.79 (m): -CO-NH-CH(C=O)-CH(N-)-S-
6.18 (m): $-CH=CH-CH_2-N^+$ E isomer
6.75 to 7.00 (m): Ar-H, -S-CH-C(C=N-)-N= and $-CH=CH-CH_2-N^+$
7.28: NH_2
7.71 (s) (2 H): H in position 2 and 3 of the imidazolium ring

8.96 (wide), 12.81 (wide) and 13.68 (wide): mobile 2 H's9.12 (s): H in position 5 of the imidazolium ring
9.47 (d) and 9.54 (d): -CO-NH-CH(C=O)-CH(N-)-S-

EXAMPLE 44: the internal salt of (±)(cis)(Z) 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] imidazo [1,2-b] pyridazinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 400 MHz, in ppm)
(1 H) masked and approximately 3.70 (d) (1 H):
-S-CH_2-C(CH=CH-)=C-
5.15 (d resolved): -CO-NH-CH(C=O)-CH(N-)-S-
5.25 to 5.45 (m): -CH=CH-CH_2-N^+ and Ar-CH(C=O)-O-
5.77 (m, d resolved after exchange): -CO-NH-CH(C=O)-CH(N-)-S-
6.25 (m): -CH=CH-CH_2-N^+ E isomer
6.65 to 6.86 (m): Ar-H and -S-CH-C(C=N-)-N=
6.96 (dl J=16Hz): -CH=CH-CH_2-N^+
7.34 (m) and 9.05 (m): mobile H's
8.00 (dd): H in position 3 of the imidazo[1,2-b]pyridazinium ring
8.54 (sl) and 8.88 (sl): H in position 6 and 7 of the imidazo[1,2-b]pyridazinium ring
8.82 (d): H in position 4 of the imidazo[1,2-b]pyridazinium ring
9.12 (d): H in position 2 of the imidazo[1,2-b]pyridazinium ring
9.55 (d) and 9.60 (d): -CO-NH-CH(C=O)-CH(N-)-S-

EXAMPLE 45: the internal salt of (±)(cis)(Z) 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2 (E)-propenyl] imidazo-[1,2-a]pyridinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)
3.55 (m) (masked): -S-CH_2-C(CH=CH-)=C-
5.15 (m): -CO-NH-CH(C=O)-CH(N-)-S-
5.29 (m): -CH=CH-CH_2-N^+
5.32 (s): Ar-CH(C=O)-O-
5.74 (m): -CO-NH-CH(C=O)-CH(N-)-S- cis isomerism

6.25 (m): $-CH=C\underline{H}-CH_2-N^+$ E isomer
6.68 to 6.92: Ar-H, $-S-C\underline{H}-C(C=N-)-N=$ and $-C\underline{H}=CH-CH_2-N^+$
7.33 (s), 9.03 (s), 9.56 (d resolved) and 12.80: mobile H's
7.57 (t) (1 H), 8.06 (t) (1 H), 8.20 (d) (1 H), 8.29 (s) (1 H), 8.45 (s) (1 H) and 8.97 (d) (1 H): H of the imidazo [1,2-a]pyridinium ring

EXAMPLE 46: The internal salt of (±)(cis)(Z) 2-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] imidazo-[1,5-a]pyridinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)
3.40 to 3.80: $-S-C\underline{H}_2-C(CH=CH-)=C-$
5.17 (m): $-CO-NH-CH(C=O)-C\underline{H}(N-)-S-$
5.18 to 5.32: $-CH=CH-C\underline{H}_2-N^+$ and $Ar-C\underline{H}(C=O)-O-$
5.76 (m): $-CO-NH-C\underline{H}(C=O)-CH(N-)-S-$ cis isomerism
6.28 (m): $-CH=C\underline{H}-CH_2-N^+$ E isomer
6.68 to 6.86: Ar-H and $-S-C\underline{H}-C(C=N-)-N=$
7.04 (d J=15.5): $-C\underline{H}=CH-CH_2-N^+$
7.29, 9.0 to 9.08, 9.54 and 12.56: mobile H's
7.19 (t) and 7.25 (t): H in position 6 and 7 of the imidazo [1,5-a]pyridinium ring
7.86 (d): H in position 8 of the imidazo[1,5-a]pyridinium ring8.23 (d): H in position 1 of the imidazo[1,5-a] pyridinium ring
9.02 (d): H in position 5 of the imidazo [1,5-a]pyridinium ring
9.74 (s): H in position 3 of the imidazo [1,5-a]pyridinium ring

EXAMPLE 47: The internal salt of [6R-[3(E), 6alpha, 7beta-[Z(R*)]]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] 6,7-dihydro 5H-pyrindinium,

Stage A: The internal salt of [6R-[3(E), 6alpha, 7beta(Z)]] 1-[3-[7-[[[[(diphenylmethoxycarbonyl) [3,4-bis[(2-methoxy ethoxy) methoxy] phenyl] methoxy] imino] [2-[(tri-phenyl-methyl) amino] 4-thiazolyl] acetyl] amino] 2-carboxy 8-oxo

5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] 6,7-dihydro 5H-pyrindinium, (R+S)

1.33 g of the iodine derivative prepared in Stage B of Example 25 and 0.585 cm^3 of cyclopentano[b]pyridine in a minimum quantity of dimethylsulphoxide (DMSO) are agitated for 5 hours, the solvent is eliminated, the residue is washed and chromatographed eluting with a dichloromethane - methanol (9-1) mixture and in this way 1.07 g of the desired product is obtained.

Stage B: The internal salt of [6R-[3(E), 6alpha, 7beta(Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] 6,7-dihydro 5H-pyrindinium,

By operating as in Stage D of Example 25, starting with 1.053 g of the product prepared in the previous stage, 1.07 g of the expected product is obtained.

Stage C: The internal salt of [6R-[3(E), 6alpha, 7beta [Z(R^*)]]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] 6,7-dihydro 5H-pyrindinium,

The product obtained in Stage B is purified by HPLC on a Microbondapack C_{18-300} (registered trademark) column of 10 microns and 0.0079 m in diameter eluting with acetonitrile with 0.025% of trifluoroacetic acid and in this way leads to the (R) and (S) isomers (See following example).

NMR of the proton (DMSO, 400 MHz, in ppm)

2.24 (m): the H's in position 6 of the 6,7-dihydro 5H-pyrindinium ring

3.15 (m) and 3.38 (masked): the H's in position 5 and 7 of the 6,7-dihydro 5H-pyrindinium ring

3.54 (d, J=17.5Hz) and 3.78 (d, J=17.5Hz): $-S-CH_2-C(CH=CH-)=C-$

5.17 (d, J=5): $-CO-NH-CH(C=O)-CH(N-)-S-$

5.32 (m): $-CH=CH-CH_2-N^+$ and $Ar-CH(C=O)-O-$

5.75 (dd, J=5Hz and J=7.5Hz): $-CO-NH-CH(C=O)-CH(N-)-S-$

6.24 (dt, J=16 and J=6.5 Hz): $-CH=CH-CH_2-N^+$ E isomer

6.70 (d, J=8Hz): H in position 6 of the 3,4-dihyroxyphenyl radical

6.74 (s): -S-CH-C(C=N-)-N=

6.75 (dd, J=1.5 and J=8Hz): H in position 5 of the 3,4-dihydroxyphenyl radical

6.86 (sl): H in position 2 of the 3,4-dihydroxyphenyl radical

6.87 (d J=16): $-CH=CH-CH_2-N^+$

7.25: Mobile NH_2's

7.90 (dd, J=6 and J=7.5): H in position 3 of the 6,7-dihydro 5H-pyrindinium ring

8.41 (d, J=7.5): H in position 4 of the 6,7-dihydro 5H-pyrindinium ring

8.75 (d, J=6): H in position 2 of the 6,7-dihydro 5H-pyrindinium ring

9.53 (d, J=7.5Hz): -CO-NH-CH(C=O)-CH(N-)-S-

8.92, 9.00, 12.76 and 13.72: mobile H's

EXAMPLE 48: The internal salt of [6R-[3(E), 6alpha, 7beta-[Z(S*)]]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] 6,7-dihydro 5H-pyrindinium,

NMR of the proton (DMSO, 400 MHz, in ppm)

2.24 (m): the H's in position 6 of the 6,7-dihydro 5H-pyrindinium ring

3.15 (m) and 3.40: the H's in position 5 and 7 of the 6,7-dihydro 5H-pyrindinium ring

3.48 (d, J=17.5Hz) and 3.63 (d, J=17.5Hz): $-S-CH_2-C(CH=CH-)=C-$

5.14 (d, J=5): -CO-NH-CH(C=O)-CH(N-)-S-

5.32 (m): $-CH=CH-CH_2-N^+$ and Ar-CH(C=O)-O-

5.78 (dd, J=5Hz and J=7.5Hz): -CO-NH-CH(C=O)-CH(N-)-S-

6.20 (dt, J=16 and J=6Hz): $-CH=CH-CH_2-N^+$ E isomer

6.68 (d, J=8Hz): H in position 6 of the 3,4-dihyroxyphenyl radical

6.75 (dd, J=2 and J=8Hz): H in position 5 of the 3,4-dihydroxyphenyl radical

6.78 (s): -S-CH-C(C=N-)-N=

6.87 (d. J=2Hz): H in position 2 of the 3,4-dihydroxyphenyl radical6.87 (d J=16): $-CH=CH-CH_2-N^+$

7.25: mobile $N\underline{H}_2$'s

7.90 (dd, J=6 and J=7.5): $\underline{H}$ in position 3 of the 6,7-dihydro 5H-pyrindinium ring

8.42 (d, J=7.5): $\underline{H}$ in position 4 of the 6,7-dihydro 5H-pyrindinium ring

8.75 (d, J=6): $\underline{H}$ in position 2 of the 6,7-dihydro 5H-pyrindinium ring

9.46 (d, J=7.5Hz): -CO-N$\underline{H}$-CH(C=O)-CH(N-)-S-

8.98 (2 H), 9.00, 12.97 (1 H) and 13.69 (1 H): mobile $\underline{H}$'s

EXAMPLE 49: the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-[(methoxy-imino) methyl] quinoleinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

3.47 (m): -S-C$\underline{H}_2$-C(CH=CH-)=C-

4.19 (s): -CH=N-OC$\underline{H}_3$ in position 4 of the quinolinium ring

5.14 (m): -CO-NH-CH(C=O)-C$\underline{H}$(N-)-S-

5.31 (s): Ar-C$\underline{H}$(C=O)-O-

5.75 (m): -CO-NH-C$\underline{H}$(C=O)-CH(N-)-S-

5.89 (m): -CH=CH-C$\underline{H}_2$-N^+

6.36 (m): -CH=C$\underline{H}$-CH_2-N^+ E isomer

6.64 to 6.77 (m): Ar-$\underline{H}$

6.85 (s,d): -S-C$\underline{H}$-C(C=N-)-N=

6.99 (d resolved j=16Hz): -C$\underline{H}$=CH-CH_2-N^+

7.31 (l): -$N\underline{H}_2$

8.09 (l) and 8.30 (t): $\underline{H}$ in position 6 and 7 of the quinolinium ring8.41 (d): $\underline{H}$ in position 3 of the quinolinium ring

8.58 (d) and 8.96 (d): $\underline{H}$ in position 5 and 8 of the quinolinium ring9.33 (s): -C$\underline{H}$=N-OCH_3 in position 4 of the quinolinium ring (E isomer)

9.52 (d,d): $\underline{H}$ in position 2 of the quinolinium ring

9.03 (l) and 9.60 (d): mobile $\underline{H}$'s

EXAMPLE 50: the internal salt of (±)(cis)(Z) 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicy-

clo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] 1-methyl pyrrolidinium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

2.10 (sl) and 3.45 (sl): H of the pyrrolidinium ring

2.99 (s): N^+-CH_3

3.9 (m): $-S-CH_2-C(CH=CH-)=C-$

4.11: $-CH=CH-CH_2-N^+$

5.18 (m): $-CO-NH-CH(C=O)-CH(N-)-S-$

5.33 (s): $Ar-CH(C=O)-O-$

5.79 (m): $-CO-NH-CH(C=O)-CH(N-)-S-$

6.17 (dt): $-CH=CH-CH_2-N^+$ E isomer

6.65 to 6.85: Ar-H and $-S-CH-C(C=N-)-N=$

7.05 (d. J=15Hz): $-CH=CH-CH_2-N^+$

EXAMPLE 51: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3 [7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-aza 1-azonia-bicyclo[2,2,2]octane (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

3.14 and 3.35: H of the 4-aza 1-azoniabicyclo[2,2,2]octane ring

3.5 to 3.95: $-S-CH_2-C(CH=CH-)=C-$

4.06: $-CH=CH-CH_2-N^+$

5.20 (d, resolved): $-CO-NH-CH(C=O)-CH(N-)-S-$

5.34 (s): $Ar-CH(C=O)-O-$

5.80 (d, resolved): $-CO-NH-CH(C=O)-CH(N-)-S-$

6.11: $-CH=CH-CH_2-N^+$ E isomer

6.7 to 6.90: Ar-H and $-S-CH-C(C=N-)-N=$

7.02 (d, resolved): $-CH=CH-CH_2-N^+$

9.10 (d resolved): $-CO-NH-CH(C=O)-CH(N-)-S-$

EXAMPLE 52: The internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 3-hydroxy 4-aza 1-azoniabicyclo[2,2,2]octane (R) or (S) or an (R+S) mixture,

Rf = 0.5 (eluant: acetone - water (4-1))

EXAMPLE 53: The internal salt of (±)(cis)(Z) 3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino]

acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0] oct-2-3-yl] N,N,N-trimethyl 2(E)-propen-1-aminium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

2.99 (s) and 3.03 (s): $-N^+(C\underline{H}_3)_3$

4.05: $-CH=CH-C\underline{H}_2-N^+$

5.16 (d): $-CO-NH-CH(C=O)-C\underline{H}(N-)-S-$

5.33 (s): $Ar-C\underline{H}(C=O)-O-$

5.76 (d): $-CO-NH-C\underline{H}(C=O)-CH(N-)-S-$

6.04 (m): $-CH=C\underline{H}-CH_2-N^+$ E isomer

6.7 to 6.90: Ar-H and $-S-C\underline{H}-C(C=N-)-N=$

7.04 (d, resolved): $-C\underline{H}=CH-CH_2-N^+$

9.08 (d resolved): $-CO-N\underline{H}-CH(C=O)-CH(N-)-S-$

EXAMPLE 54: The internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N-dimethyl N-(2-hydroxy ethyl) 2-propen-1-aminium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

3.05 (s): $-N^+(C\underline{H}_3)_2-CH_2-CH_2-OH$

3.38 and 3.87: $-N^+(CH_3)_2-C\underline{H}_2-C\underline{H}_2-OH$

4.14 (d): $-CH=CH-C\underline{H}_2-N^+$

5.19 (d, resolved): $-CO-NH-CH(C=O)-C\underline{H}(N-)-S-$

5.80 (d, resolved): $-CO-NH-C\underline{H}(C=O)-CH(N-)-S-$

6.14: $-CH=C\underline{H}-CH_2-N^+$ E isomer

6.87: $-S-C\underline{H}-C(C=N-)-N=$

6.65 to 6.80: Ar-H

7.03 (d, resolved): $-C\underline{H}=CH-CH_2-N^+$

7.36 and 9.05: $-O\underline{H}$

9.59 (d resolved): $-CO-N\underline{H}-CH(C=O)-CH(N-)-S-$

EXAMPLE 55: The internal salt of (±)(cis)(Z) N-(2-amino 2-oxo ethyl) 3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N-dimethyl 2(E)-propen-1-aminium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

3.19 (s): $-N^+(C\underline{H}_3)_2-CH_2-CO-NH_2$

4.01 (s): $-N^+(CH_3)_2-C\underline{H}_2-CO-NH_2$

4.27 (d): $-CH=CH-C\underline{H}_2-N^+$
5.19 (d): $-CO-NH-CH\ (C=O)-C\underline{H}(N-)-S-$
5.34 (s): $Ar-C\underline{H}(C=O)-O-$
5.85 (m): $-CO-NH-C\underline{H}(C=O)-CH(N-)-S-$
6.13: $-CH=C\underline{H}-CH_2-N^+$ E isomer
6.72 to 6.80: Ar-H and $-S-C\underline{H}-C(C=N-)-N=$
7.03: $-C\underline{H}=CH-CH_2-N^+$
7.33, 7.70, 7.94 and 9.04: mobile H's
9.55 (d) and 9.62 (d): $-N\underline{H}-$

EXAMPLE 56: the internal salt of (±)(cis)(Z) 3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0] oct-2-en-3-yl] N-(cyanomethyl) N,N-dimethyl 2(E)-propen-1-aminium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)
3.19 (s): $-N^+(C\underline{H}_3)_2-CH_2-CN$
4.24 (d): $-CH=CH-C\underline{H}_2-N^+$
4.8 (s): $-N^+(CH_3)_2-C\underline{H}_2-CN$
5.20 (d): $-CO-NH-CH(C=O)-C\underline{H}(N-)-S-$
5.33 (s): $Ar-C\underline{H}(C=O)-O-$
5.82 (m): $-CO-NH-C\underline{H}(C=O)-CH(N-)-S-$
6.13 (m): $-CH=C\underline{H}-CH_2-N^+$ E isomer
6.65 to 6.80: Ar-H
6.87: $-S-C\underline{H}-C(C=N-)-N=$
7.10: $-C\underline{H}=CH-CH_2-N^+$
7.79 (2 H), 9.07 (2 H): mobile H's
9.54 (d): $-CO-N\underline{H}-CH(C=O)-CH(N-)-S-$

EXAMPLE 57: The internal salt of (±)(cis)(Z) 3-[7-[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]-oct-2-en-3-yl] N,N-dimethyl N-[(2-methoxyimino) ethyl] 2(E)-propen-1-aminium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)
3.19 (s): $-N^+(C\underline{H}_3)_2-CH_2-CH=N-O-CH_3$
3.89 (s): $-N^+(CH_3)_2-CH_2-CH=N-O-C\underline{H}_3$
4.10 to 4.30 (m): $-CH=CH-C\underline{H}_2-N^+$ and $-N^+(CH_3)_2-C\underline{H}_2-CH=N-O-CH_3$
5.20 (d): $-CO-NH-CH(C=O)-C\underline{H}(N-)-S-$
5.35 (s): $Ar-C\underline{H}(C=O)-O-$

5.81 (m,d resolved after exchange): -CO-NH-CH(C=O)-CH(N-)-S-
6.14 (m): -CH=CH-CH_2-N^+ E isomer
6.7 to 6.88: Ar-H and -S-CH-C(C=N-)-N=
7.04: -CH=CH-CH_2-N^+
7.77 (m): -$N^+(CH_3)_2$-CH_2-CH=N-O-CH_3
9.57 and 9.65: -CO-NH-CH(C=O)-CH(N-)-S-

EXAMPLE 58: the internal salt of (±)(cis)(Z) 1-[3-[7--[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] imidazo [1,2-a] pyrimidin-4-ium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)
3.66 (m) (masked): -S-CH_2-C(CH=CH-)=C-
5.14 (d, resolved): -CO-NH-CH(C=O)-CH(N-)-S-
5.24 (m): -CH=CH-CH_2-N^+
5.31 (s): Ar-CH(C=O)-O-
5.74 (m): -CO-NH-CH(C=O)-CH(N-)-S- cis isomerism
6.23 (m): -CH=CH-CH_2-N^+ E isomer
6.65 to 6.84 (4 H): Ar-H, and -S-CH-C(C=N-)-N=
6.94 (d, resolved J=16): -CH=CH-CH_2-N^+
7.31 (sl): -NH2
9.03 (m): mobile H's
7.76 (dd) (1 H): H in position 6 of the imidazo[1,2-a]-pyrimidin-4-ium ring
8.39 (s): H in position 2 and 3 of the imidazo[1,2-a]-pyrimidin-4-ium ring
9.14 (d, resolved) (1 H): H in position 7 of the imidazo-[1,2-a]pyrimidin-4-ium ring
9.39 (d, resolved) (1 H): H in position 5 of the imidazo-[1,2-a]pyrimidin-4-ium ring

Unless otherwise indicated, the products of Examples 31 to 58 mentioned previously were prepared by the method described in Example 25, using the corresponding nitrogenous base.

EXAMPLE 59: Preparations for injections of the following formula were prepared:

- Product of Example 31. ..... 500 mg
- Sterile aqueous excipient sufficient quanitity for ..... 5 cm^3

PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION

Activity in vitro, method of dilutions in solid medium.

A series of dishes are prepared in which the same quantity of sterile nutrient medium is distributed, containing increasing quantities of the product to be studied, then each dish is sown with several bacterial strains.

After incubation for 24 hours in an incubator at 37°C, the growth inhibition is evaluated by the absence of any bacterial development, which allows the minimum inhibiting concentrations (MIC) expressed in micrograms/cm^3 to be determined.

The results are expressed in MIC_{90} which is the minimum concentration of antibiotic causing growth inhibition in 90% of the strains studied.

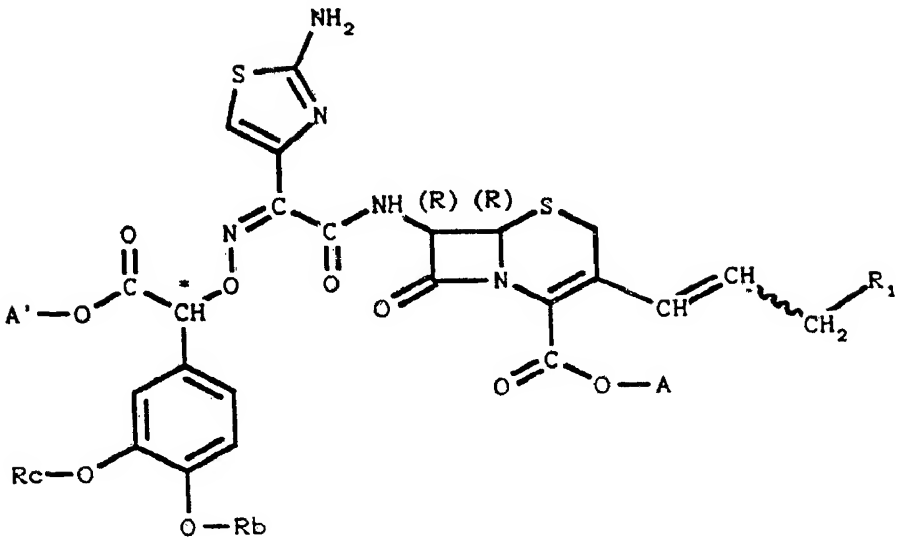
The following results were obtained:

Number of strains / Compound example	Enterobacteria		Staphylococcus aureus oxacilline S	Proteus SPP	Pseudomonas Aeruginosa
	Cefotax.S 27	Cefotax.R 40	20	9	40
2	0,3	5	0,6	0,15	1,25
4	0,3	5	1,25	0,3	5
9	0,6	10	1,2	0,6	2,5
12	0,3	10	0,6	0,3	10
16	0,6	10	1,2	0,6	2,5
17	0,6	10	1,2	0,6	1,2
18	0,15	2,5	0,3	0,3	2,5

Product of Example	Enterobacteries Cloacae 1321E	Staphylococcus aureus SG 5 11	Proteus A 235	Pseudomonas Aeruginosa 1771 m
29	0.08	0.15	0.04	0.3
31	0.04	0.15	0.02	0.6
25	0.15	0.15	0.02	0.15
45	0.15	0.15	0.04	0.6

The claims defining the invention are as follows:

1.- The products of general formula (I):

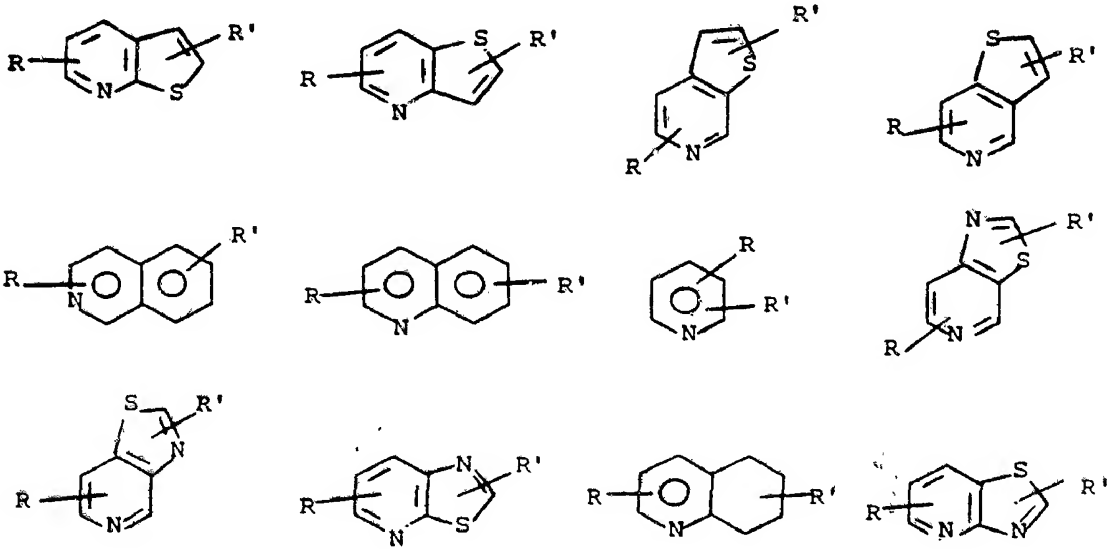


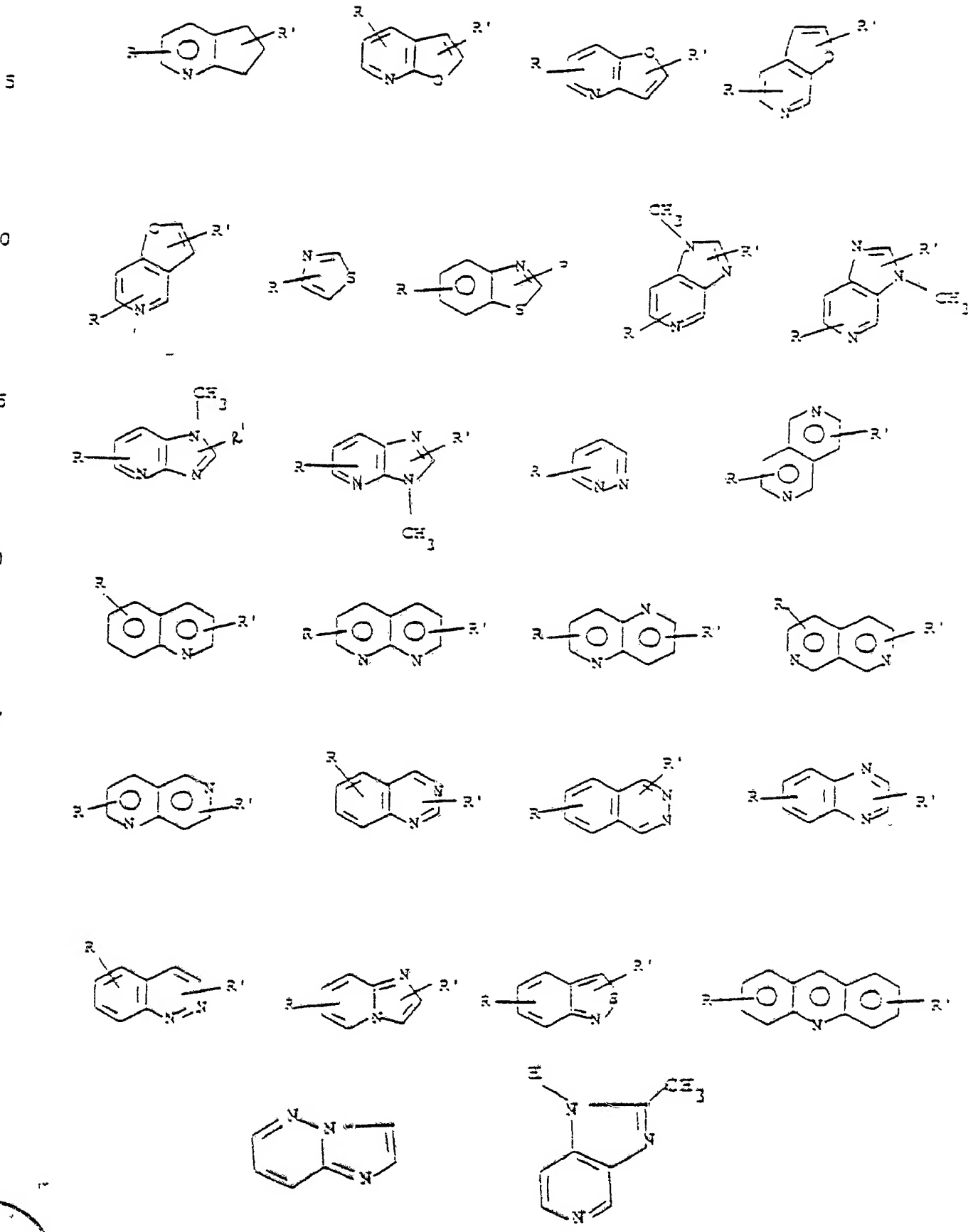
(I)

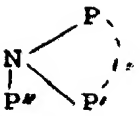
SYN isomer

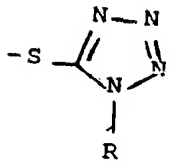
syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:

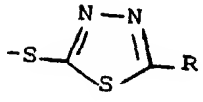
R_1 represents a radical chosen from the following radicals:



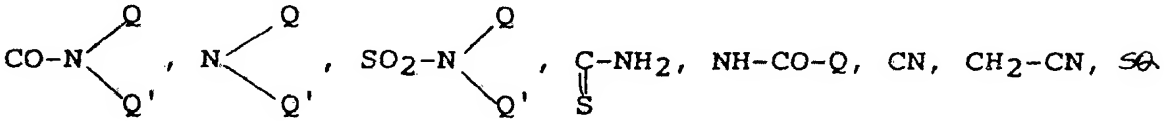


or  in the quaternary ammonium form or





in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a CO_2-Q,

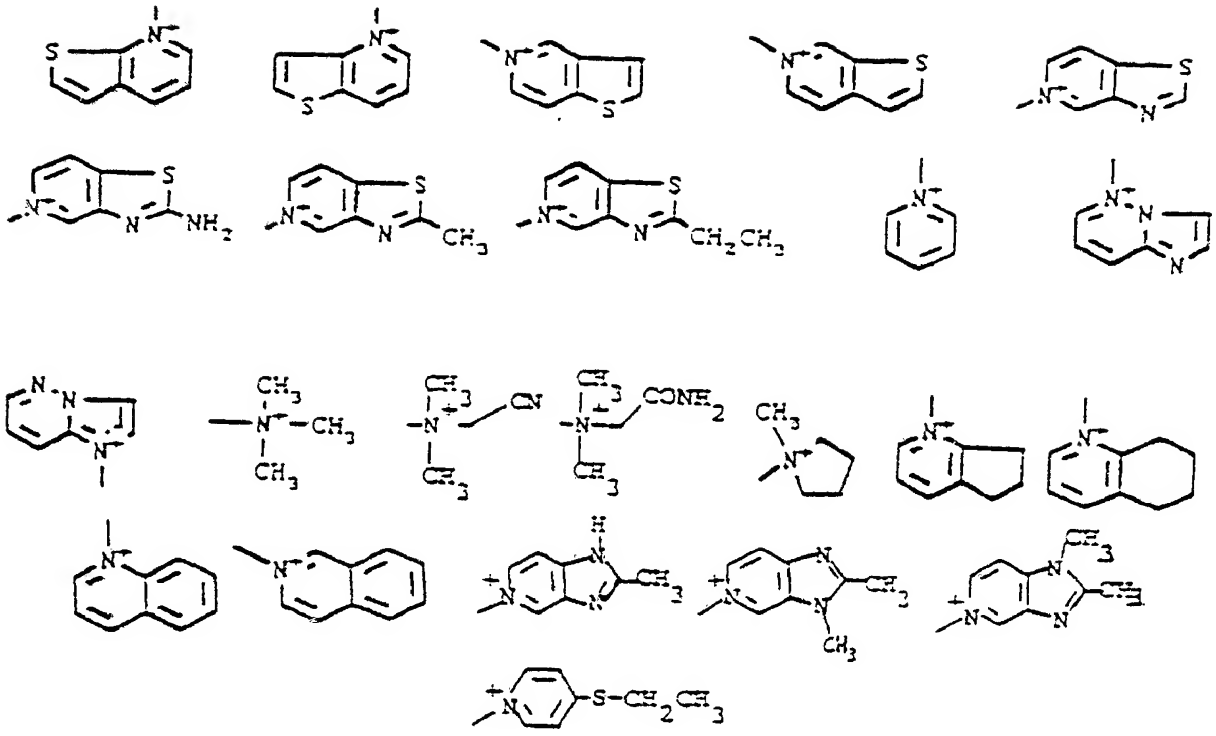


CH_2-SQ in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P '', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, a saturated heterocycle with 5 or 6 links.

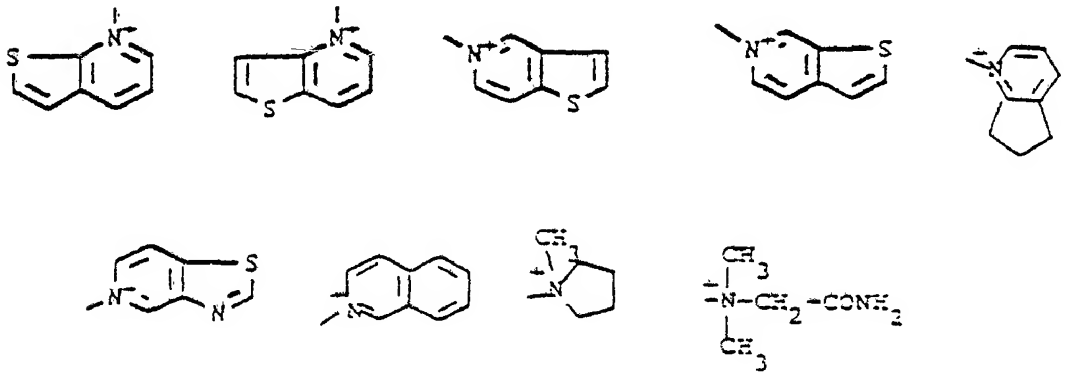
R_b and R_c, identical or different, represent a hydrogen atom or an acyl group,

A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A' represent the remainder of an easily cleavable ester group or CO_2A represents $CO_2^{\ominus}$; the wavy line means that the CH_2R_1 group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids.

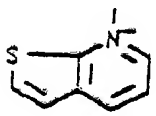
2.- The products of general formula (I) as defined in claim 1 in which R_1 is chosen from the following radicals:



3.- The products of general formula (I) as defined in claim 1 or 2 in which R_1 is chosen from the following radicals:



preferably the radical:



4.- The product of general formula (I) according to claim 1 of which the name follows:

- [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E),6alpha, 7beta(Z)]]-7-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters and particularly in the S form,

- [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl] isoquinolinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

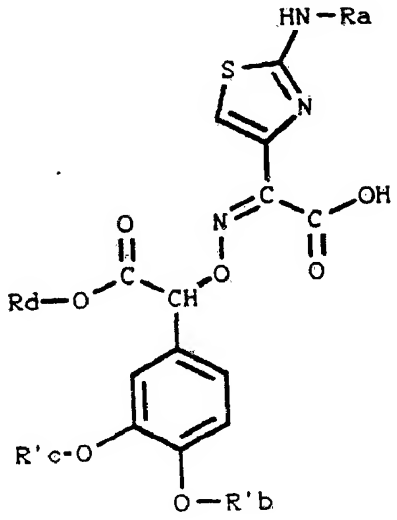
- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium in the R or S form or the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-

[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyrindinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-3-[7-[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters.

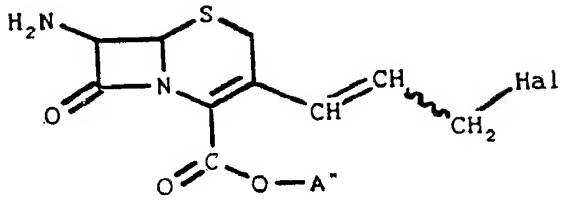
5.- Preparation process for the products of formula (I) as defined in claim 1, characterized in that a product of formula (II):



(II)

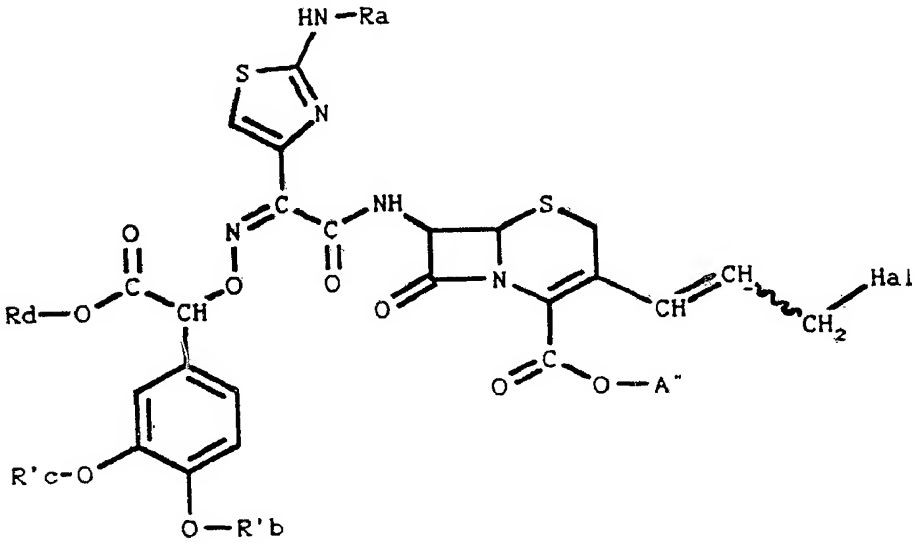
racemic or optically active syn isomer or a functional derivative of the product of formula (II), in which R_a represents a hydrogen atom or a protective group of the amino radical, R'_b and R'_c, identical or different, represent a hydrogen atom or a protective group of the hydroxyl radical, R_d represents a hydrogen atom or the remainder of an easily

eliminable ester group, is reacted with a product of formula (III):



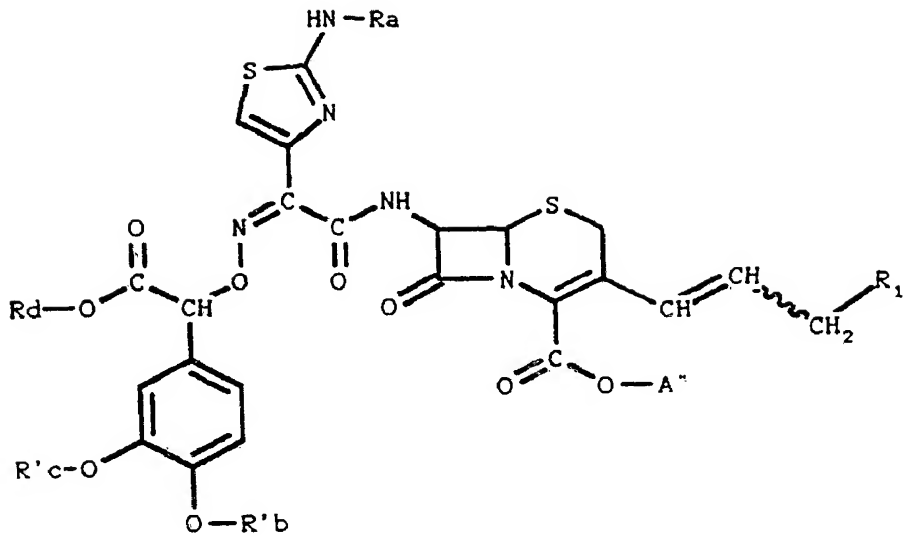
(III)

in which Hal represents a halogen atom, A" represents a hydrogen atom or the remainder of an easily eliminable ester group and the wavy line indicates that the CH_2Hal group can be found in E or Z position, in order to obtain a product of formula (IV):



(IV)

which is reacted with a reagent capable of introducing the R_1 radical in order to obtain a product of formula (V):



(V)

which, if desired, is separated into its E or Z isomers or the Z isomers are converted into E isomers and which products of formula (V), if necessary or if desired, are subjected to one or more of the following reactions, in any order:

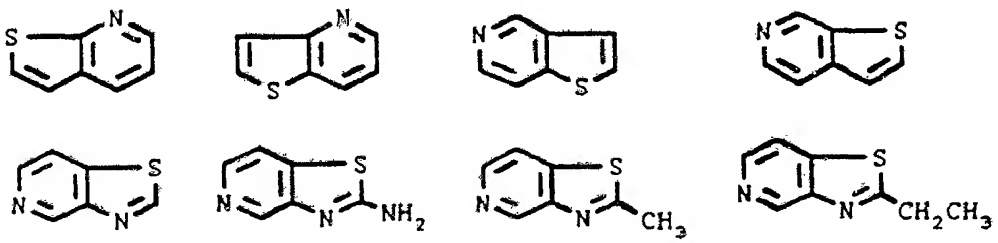
a) cleaving, by hydrolysis or by the action of the thiourea, of all or part of the ester groups or protective groups of the amino radical or the hydroxyl radicals,

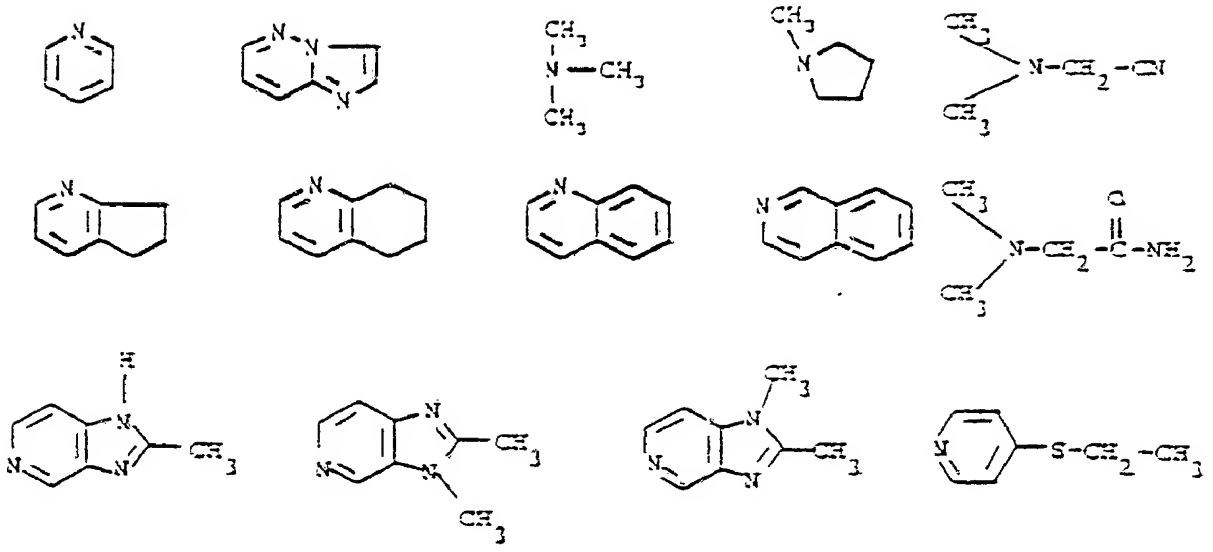
b) esterification or salification of the carboxylic radical or radicals by a base,

c) salification of the amino radical by an acid,

d) separation of products in the form of an R, S mixture into R or S.

6.- Preparation process according to claim 5 characterized in that the reagent capable of introducing the R_1 radical is chosen from the reagents of formulae:





7. Preparation process according to claim 5, wherein R_a represents a protective group of the amino radical in the products of formula (IV) and the products of formula (V).

8. Preparation process for the products of formula (I) as defined in claim 1 which process is substantially as herein described with reference to any one of the Examples.

9. Products of formula (I) whenever prepared by the process of any one of claims 5 to 8.

10. Products of general formula (I) as defined in claim 1, substantially as herein described with reference to any one of the Examples.

11. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 4 together with a pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

12. A pharmaceutical composition as defined in claim 11, substantially as herein described with reference to Example 59.

13. ~~A method of treating affections caused by sensitive germs notably staphylococcis in a patient/mammal requiring such treatment which method~~

13. The compound of formula (IV) and the compound of formula (V) as claimed in claim 5, in which R_a represents a protective group of the amino radical.

14. A method of treating affections caused by sensitive germs notably staphylococcis in a patient/mammal requiring such treatment which method comprises administering to said patient/mammal an effective amount of a compound of formula (I) as defined in any one of claims 1 to 4 or a composition as defined in claim 11 or claim 12.

15. The method according to claim 14, wherein said affections include staphylococcus septicemia, malignant staphylococcis of the face or skin, pyodermitis, septic or suppurating wounds, anthrax, phlegmons, erysipelas, acute primitive or post-influenza staphylococcis, bronchopneumonia, lung suppurations.

16. A method of treating affections caused by gram (-) bacteria in a patient/mammal requiring such treatment which method comprises administering to said patient/mammal an effective amount of a compound of formula (I) as defined in any one of claims 1 to 4 or a composition as defined in claim 11 or claim 12.

17. The method according to claim 16, wherein said affection includes colibacillosis.

DATED this 28th day of January 1994.

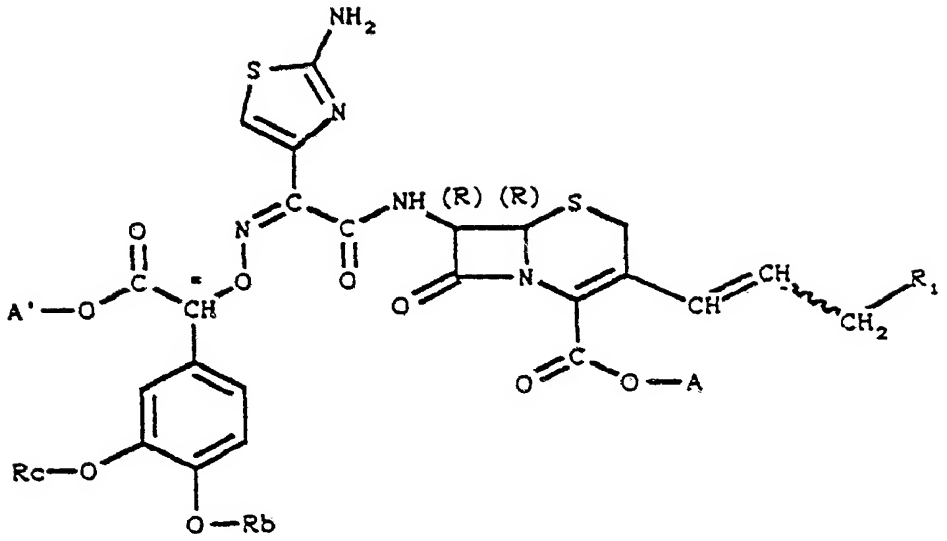
ROUSSEL-UCLAF

By their Patent Attorneys:

CALLINAN LAWRIE

Abstract

Cephalosporins of general formula (I):

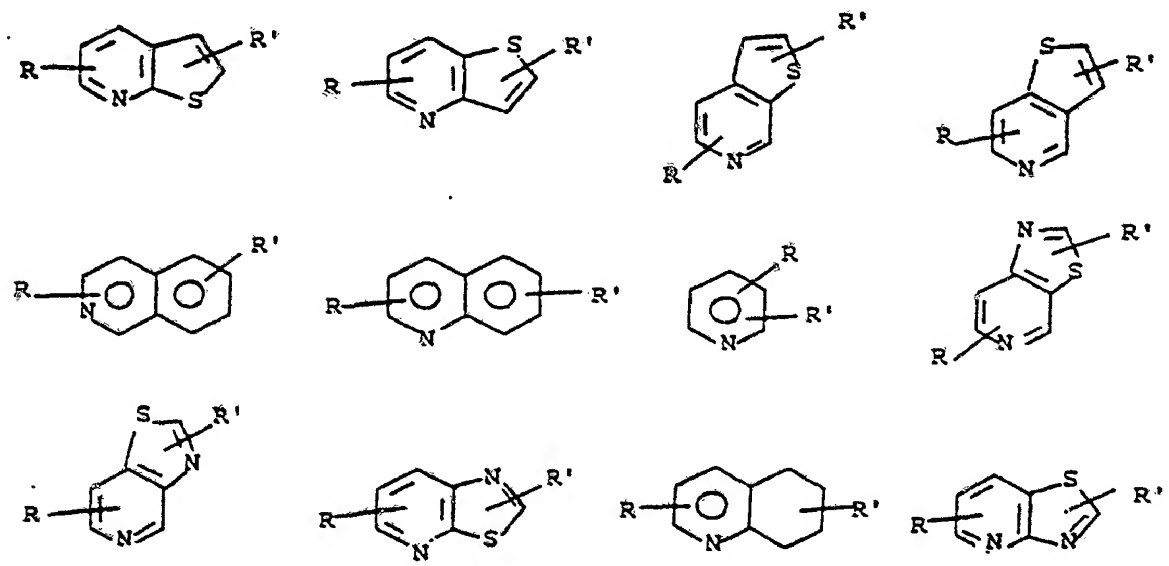


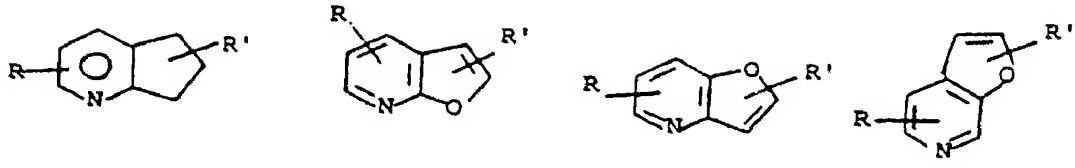
(I)

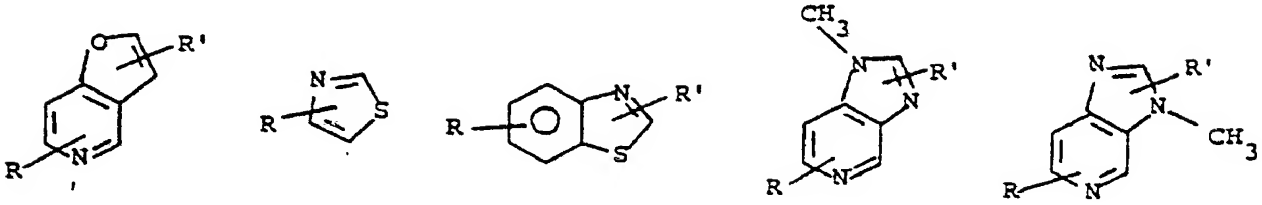
SYN isomer

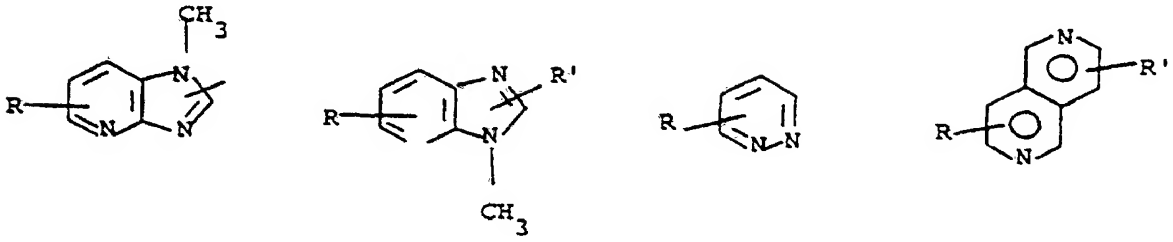
<u>syn</u> isomer, in R or S form or in the form of an R, S, mixture, formula in which:

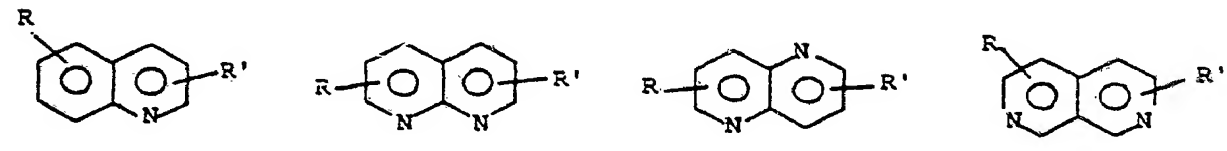
R_1 represents a radical chosen from the following radicals:

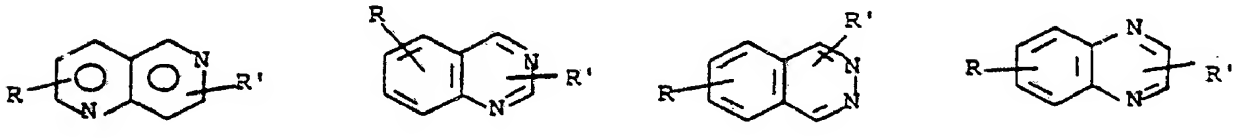


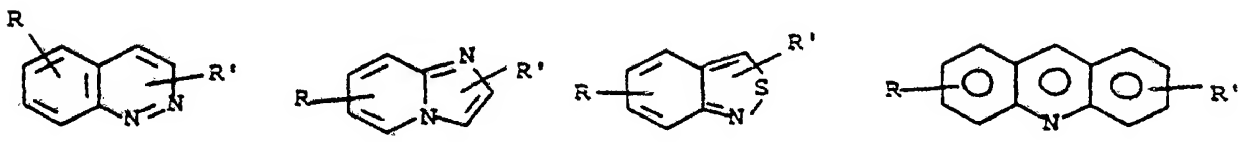


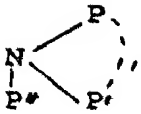


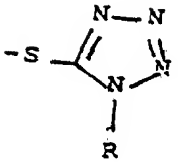


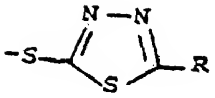


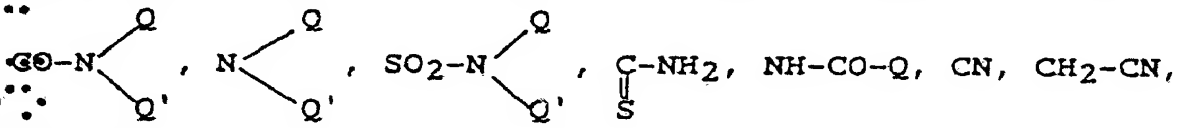




or  , in the quaternary ammonium form or





in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a CO_2-Q,  CH_2-SQ in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P '', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, a heterocycle with 5 or 6 links.

R_b and R_c, identical or different, represent a hydrogen atom or an acyl group,

A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A' represent the remainder of an easily cleavable ester group or CO_2A represents $CO_2^{\ominus}$; the wavy line means that the CH_2R_1 group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids,

their preparation process, their use as medicaments, the compositions containing them and the new intermediates obtained.